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Studies on 3-azabicyclo [3.3.1] nonanones derivatives: A mini Review

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Abstract
This review describes the recent literature surveyed regarding the synthesis of 2,4-diaryl-3-azabicyclo[3.3.1]nonanone (3-ABNs) and their biological activities in the last six years (2008-2014). These heterocyclic compounds are obtained from the Mannich reaction of ketones, aldehydes and ammonium acetate in polar aprotic solvents. The carbonyl group enables the functionalization of 3-ABNs into sulphur and nitrogen containing heterocycles such as hydrazones, oximes, hydrazide, thiazoles, amides and semicarbazones. The 3-ABNs heterocycles exist in chair-chair and/or boat-chair conformations with equatorial phenyl groups. From the surveyed literature studies the major importance was given to their biological activities against the different fungal and bacterial strains. The structure activity relationship indicated that electron withdrawing groups at the *ortho* and *para* position of the aryl rings enhanced the antibacterial and antifungal activities.

Keywords: 2,4-diaryl-3-azabicyclo[3.3.1]nonanone, Mannich reaction, Chair-Chair, Antibacterial, Antifungal

1. Introduction
The 3-azabicyclonone pharmacophore is present in naturally occurring diterpenoid/norditerpenoid alkaloids, which are isolated from a range of plants including aconitum, delphinium, consolida and thalictrum species [1-3]. Heterocyclic molecules bearing 3-azabicyclonone nucleus are of importance due to their diverse biological properties, such as analgesic and anesthetic [4-6] antibacterial, antifungal, microbicidal [7, 8], herbicidal, insecticidal, anti-inflammatory, anticancer, depressant activities [2, 9-11] and human serotonin 5-HT3 receptor and calcium antagonistic activities [12]. Tropane, cocaine and granatane are some of the azabicyclo alkaloids found in pharmacologically and medicinally active drugs [3, 6, 13].
The synthesis, stereochemistry, reactions and brief biological activities of 3-azabicyclo [3.3.1] nonanones (3-ABNs), 3,7-diazabicyclo[3.3.1]nonanones, 3,9-diazabicyclo[3.3.1] nonanones, 3-oxa-7-azabicyclo[3.3.1] nonanones and 3-thia-7-azabicyclo[3.3.1] nonanones were reviewed in 1981 [2]. Hence this mini-review describes the synthesis and highlights the significant biological activities of 3-azabicyclo[3.3.1] nonanones reported in the last six years. Figure 1 shows structures of 3-azabicyclo[3.3.1] nonan-9-ones **A** which are derivatives of bicyclic ketones, bicyclo(3.3.1) nonan-9-ones **B**.

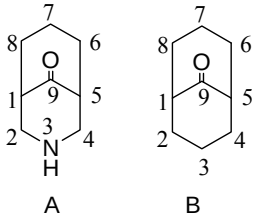
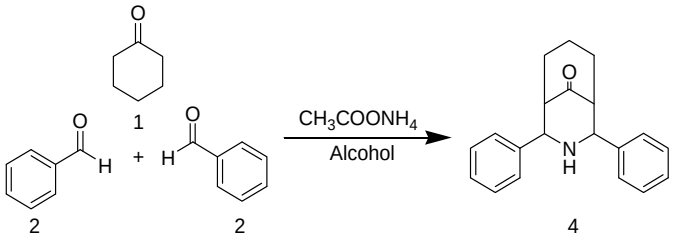


Figure 1 3-azabicyclonones

2. Discussion
2.1 Synthetic strategy
The general synthetic strategy towards 2,4-diaryl-3-azabicyclo[3.3.1]nonanones **4** is based on a three component Mannich reaction of cyclohexanone (or any ketone with four α-hydrogens)

1, aryl-aldehyde **2** and ammonium acetate [7, 8, 14-18] as shown in Scheme 1. The optimized reaction conditions involve using the reagents in mole ratios of 1:2:1.5, stirred at 30-35 °C and avoiding ether during the reaction work up [19]. The 1.5 equivalence of NH_4OAc to 1 mol of cyclohexanone prevents the formation of the chalcone by-product, while the addition of ether leads to loss of the product.

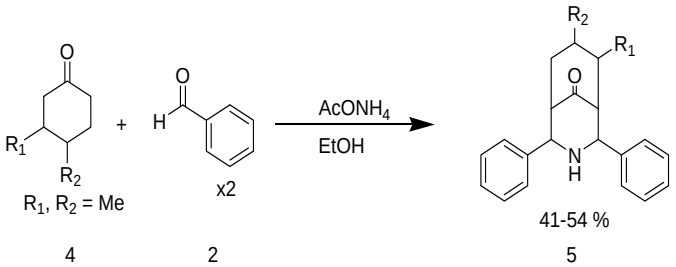


Scheme 1

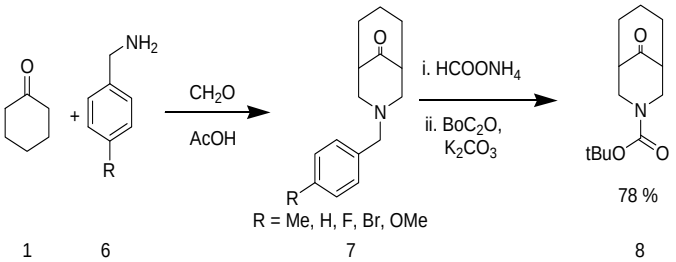
2.2 Synthesis of 2,4-diaryl-3-azabicyclo[3.3.1]nonanones

Methyl substituted cyclohexanones **4** were employed to prepare 3-ABNs bearing a methyl group at position C-6 or C-7. The methyl group substituents did not exert any influence on the yields, as the target compounds **5** were reported in low yields, 41-54 %[16,20], Scheme 2. *Tert*-butyl carboxylate 2,4-diaryl-3-azabicyclo[3.3.1]nonanones **8** were derived by the dealkylation of benzylamines **7** using ammonium formate followed by acylation, Scheme 3 [21].

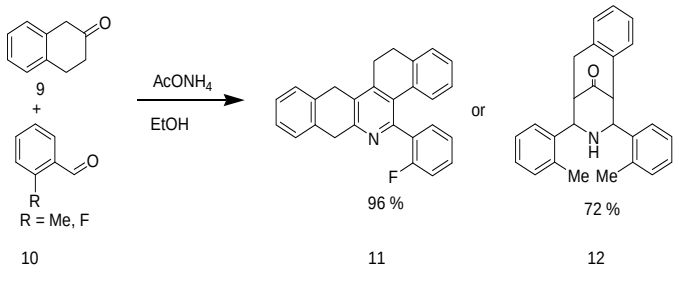
The green synthetic methodologies are always worth pursuing, thus a microwave assisted synthesis was reported using the general synthetic strategy reagents **1** and **2** irradiated at 240 watts for 2-3 minutes. To obtain better yields (65-68 %) the reaction mixtures were kept in ether for one or two days [14, 22] have reported that the Mannich reaction using 2-tetralone **9** either yields phenanthridines **11** or 3-ABNs **12** depending on the aldehyde *ortho*-substituent. The *ortho*-methyl group yields 3-ABNs while the fluro-group afforded phenanthridines, Scheme 4. Karthikeyan and co-workers [22] reported zero yield for 3-ABNs when using 4-ethoxybenzaldehyde **13**, which contrasted Parthiban and co-workers [20] results who reported the 74% 3-ABNs yield. The differences on the reaction products was attributed to raising the reaction temperature to 35 °C from room temperature by the Parthiban group [20], Scheme 5.



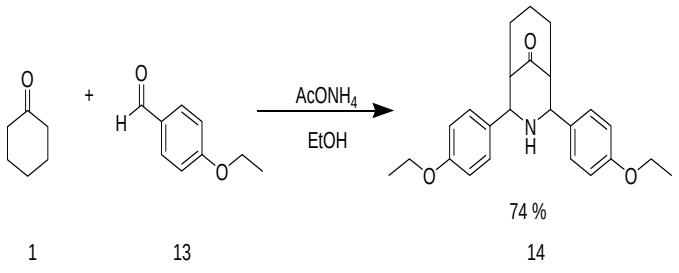
Scheme 2



Scheme 3



Scheme 4



Scheme 5

3. Functionalized 3-azabicyclo[3.3.1]nonanones

The presence of the carbonyl group in 3-azabicyclonones affords the opportunity to substitute the oxygen with nucleophilic nitrogen from amines, hydrazine and azides. The 3-ABNs were converted to oximes **15**, **16** and oxime ethers **17** using hydroxylammonium chloride or methoxyammonium chloride and benzyloxyammonium chloride [7, 17], Scheme 6.

The 3-ABNs hydrazones **18** were synthesized from the reaction of 2,4-diaryl-3-azabicyclo[3.3.1]nonanones **3** and 4-aminobenzoic acid hydrazide, Scheme 7. The 3-ABNs reacted with 4-phenylthiosemicarbazide to afford thiosemicarbazones **19** [18]. The electron donating groups afforded higher yields than the electron withdrawing groups, irrespective of their position on the phenyl rings. The 2,4-diphenyl-3-azabicyclo[3.3.1]nonanone *O*-nicotinoyl oxime **20** was synthesized through the reaction of 2,4-diphenyl-3-azabicyclo[3.3.1]nonanone oxime **16** and nicotinic acid in the presence of pyridine and $POCl_3$, Scheme 7 [23].

Ramachandran and co-workers cyclized thiosemicarbazones **22** to 1,3-thiazolidin-4-ones **23** using ethyl bromoacetate [24], Scheme 8. The thiosemicarbazones were also cyclized with phenacyl bromide to afford Hantzsch thiazoles **21**, Scheme 8[25]. Good yields were obtained in polar aprotic solvents.

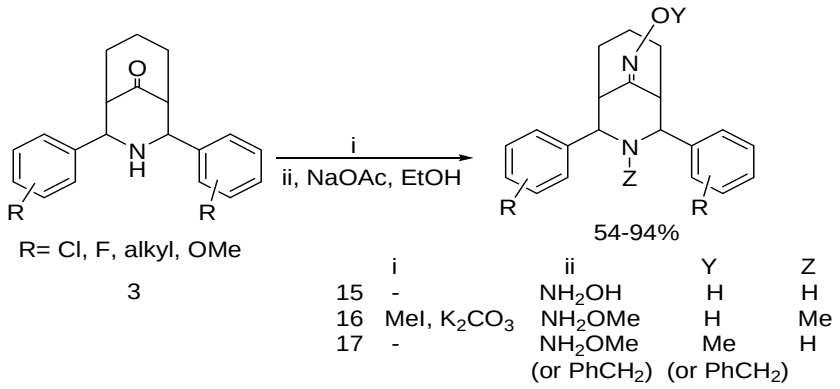
The thiosemicarbazones **22** were further cyclized under microwave irradiations to yield 1,2,4-triazolidin-3-thiones **24** [26] instead of 1,3-thiazolidin-4-ones **23** [24]. The cyclization of 3-ABNs in acetic anhydride afforded 1,3-thiazolidin-4-ones **25** containing two nitrogen atoms in the thiazole ring. The electron withdrawing groups yields (75-90 %) were higher than the electron donating groups (60-65 %) yields [27], Scheme 9.

Acetyl and propionyl group substituted *spiro* thiadiazole derivatives **27** and **28** were reported *via* the cyclization of 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones **26**, Scheme 10. The acetylation or propionylation of NH group does not have a significant effect on the yields [28].

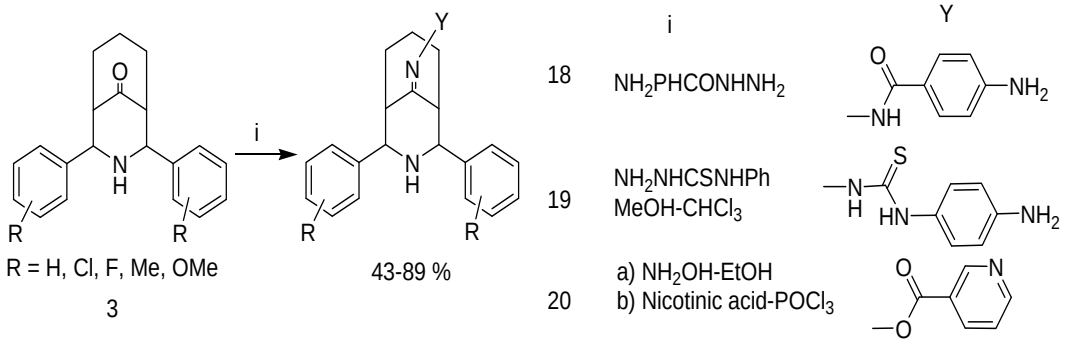
Urea based 3-ABNs were derived from 3-ABNs based amine **29** and *N*-succinimidyl carbamate **30**, while the amides **31** were obtained *via* benzoylation using 2,5-dimethylbenzoyl chloride derivatives in the presence of triethylamine [9, 29], Scheme 11.

The 3,7-dihetero analogues of 2,4-diaryl-3-azabicyclo[3.3.1]nonanones **32** have also been reported [15, 30],

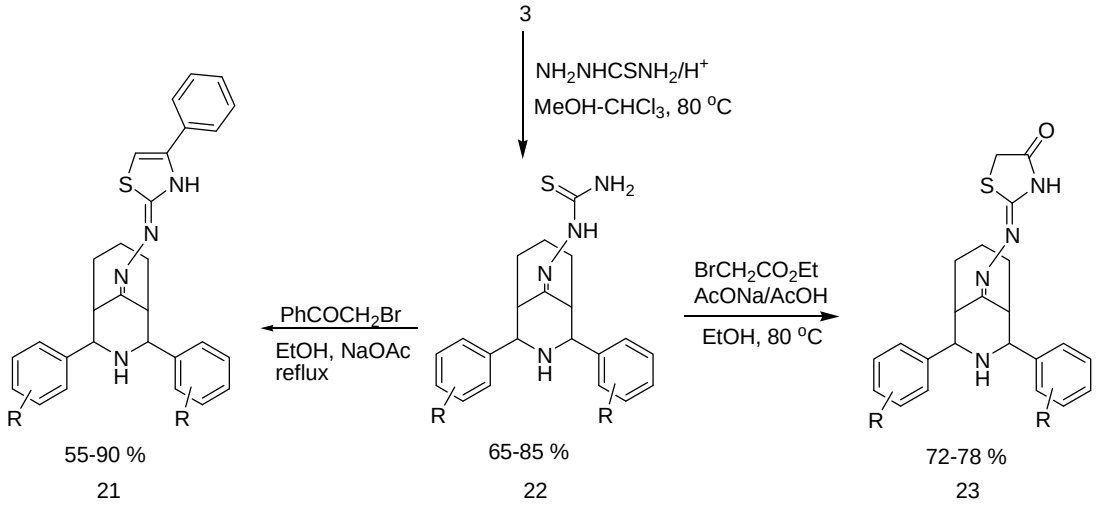
The 3,7-diazabicyclononanones were synthesized by replacing cyclohexanone with acetone in the general method[20], which afforded symmetrically substituted 3,7-diazabicyclononanones **33** and their oximes, Figure 2.



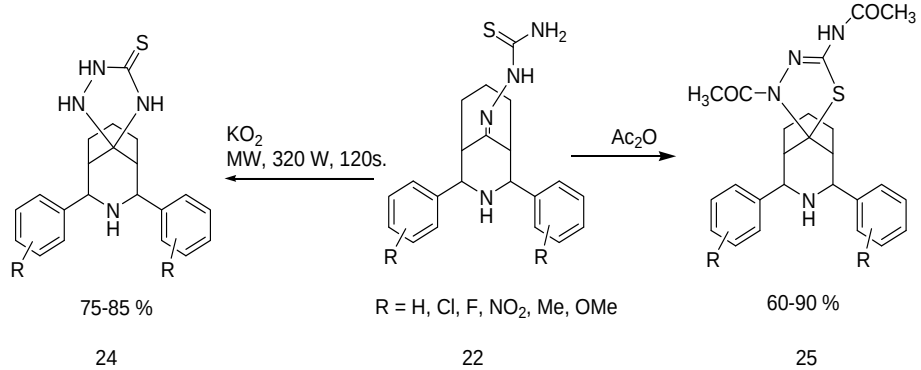
Scheme 6



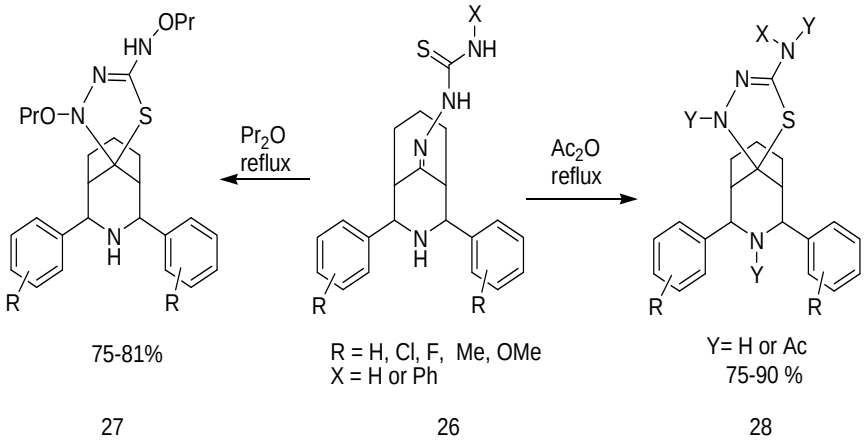
Scheme 7



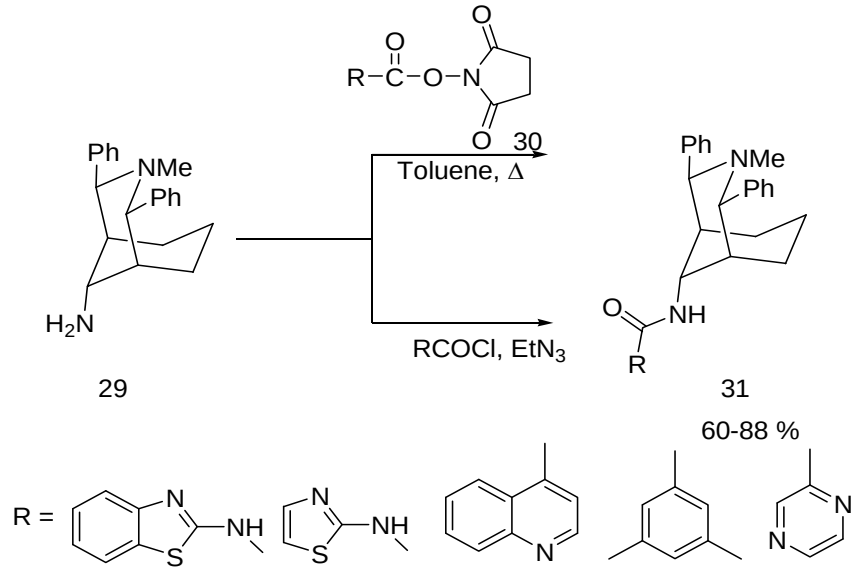
Scheme 8



Scheme 9



Scheme 10



Scheme 11

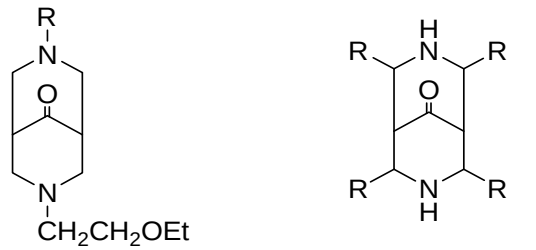


Figure 2

4. Conformations

Since the biology of a molecule can be determined by its stereochemistry, the 3-azabicyclo[3.3.1]nonanone pharmacophore has been widely studied to establish its preferred conformations. The reported NMR analysis has led to conclusions that 3-azabicyclo[3.3.1]nonanone prefers a twin-chair conformation, Figure 3, having equatorial orientations of the phenyl groups at C-2 and C-4, regardless of either linear or bulkier substituents on the phenyl ring or methyl groups on the heterocycle or carbocycle [8, 15-17]. These conclusions were also supported by crystal data [7]. NOE correlations exist between H-1/H-2, H-1/H_a-8, H-1/H_a-6, H-2/H-4, H-4/H-5, H_a-6/H_e-8, H_a-6/H_e-7. Long range '*W*' couplings were evident between H-1/H-5, H_a-6/H_a-4 and H_a-8/H_a-2. The boat-chair conformer was suggested for compounds having a methyl at C-7 and for 3,7-diazabicyclo[3.3.1]nonan-9-ones[7,15,20]. In the boat-chair the key NOE correlations are observed between H_e-6/H-7 and H-1/H-7. The methyl on the boat-chair conformers has an exocyclic orientation [7].

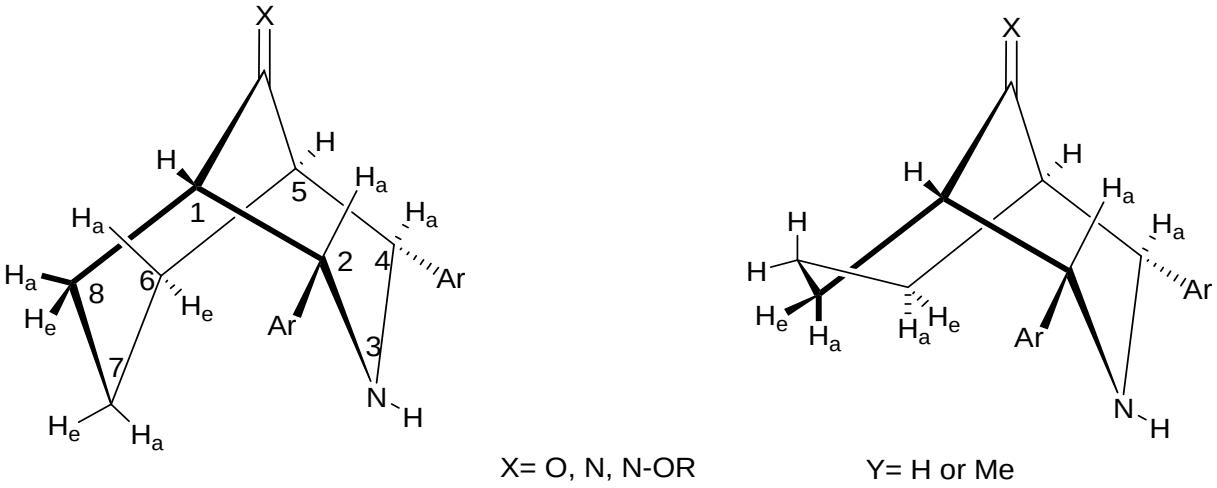


Figure 3
chair-chair (**A**) and boat-chair (**B**)

5. Biological activities

The significant reported biological activities (MIC = ≤ 25 µg/mL) are shown in Table 1. Literature shows that the antibacterial and antifungal activities are influenced by the aromatic substituents. The electron withdrawing substituents in the aromatic rings shows greater activity [7, 8, 17, 18, 26, 27]. The chloro, bromo and fluro groups at *ortho* and *para* positions exert higher activities compared to the methoxy and alkyl groups. Figure 4-7 shows the chemical structures of compounds reported in Table 1.

Compounds **81** and **83** exhibited poor DPPH radical scavenging activity (2.4-3.6 % Inhibition). The electron donating groups (MeO, alkyl/alkoxy) did not impart good antioxidant activities on 3-ABNs oximes as would be expected [19]. Compounds **81** and **83** indicated good *in vitro* antituberculostic activity against M. tuberculosis H37Rv. Oxime **81** registered 16 mm inhibition zone while **83** showed excellent activity with 21 mm inhibition zone, which was similar to that of the standard, isoniazid [19]. In the literature, there are no reports of any of the 3-ABNs being on clinical trial as antimicrobials. Compound **88** showed peripheral analgesic activity in a hot plate test [29].

6. Conclusion

The 2,4-diaryl-3-azabicyclo[3.3.1]nonanone are accessible *via* a three component Mannich reaction of cyclohexanone (or a ketone with four α-hydrogens), aldehyde and ammonium acetate in 1:2:1.5 mole ratios. Good yields were reported when the reactions were warmed in polar aprotic solvents. The surveyed reports agreed on the preference of 3-ABNs for the chair-chair and/or boat-chair conformations irrespective of the substitution pattern. A general trend for good antibacterial and antifungal activities was of the order F > Cl > methyl > methoxy. The *ortho*/*para* positions are the favoured phenyl substituent positions for good activities and this shows the role of substituent's electronic effects in enhancing the activities of 3-azabicyclononane. The 3-ABNs show poor to moderate DPPH radical scavenging activities. The surveyed reports mostly reports on antimicrobial activities, but given the ease of access of 2,4-diaryl-3-azabicyclo[3.3.1]nonanone, the reported compounds could still be evaluated for many other biological activities such as anticancer, anti-inflammatory, enzyme inhibitors, metal chelation and insecticidal properties. These are activities reported for the hybrid structures of oximes, thiazoles and amides.

7. Acknowledgments

The Author's would like to thank the University of Botswana Library, for assistance with the literature search.

Table 1: Antibacterial and antifungal activities of reported 3-ABN derivatives

3-ABNs	Minimum Inhibitory Concentration (µg/mL)										
	Sa	***Bs***	***St***	***Ec***	***Kp***	***Ca***	***Ro***	***An***	***Af***	***Cn***	***Ref***
34	-	-	-	-	12.5	-	-	-	-	6.25	a
35	-	-	-	25	-	6.25	25	-	-	-	a
36	-	-	-	-	-	-	-	12.5	-	-	a
37	-	-	-	25	n-	6.25	25	-	-	-	a
38	-	-	-	12.5	-	-	-	25	-	-	a
39	-	-	-	-	12.5	25	25	-	-	-	a
40	-	-	-	-	-	6.25	-	-	-	-	a
41	-	25	-	-	-	-	-	-	-	-	b
42	12.9	-	25	-	-	-	-	-	-	-	c
43	12.5	12.5	12.5	12.5	25	12.5	12.5	12.5	-	-	c
44	-	25	6.25	6.25	6.25	25	12.5	25	6.25	25	c
45	25	-	25	12.5	-	25	-	25	-	6.25	c
46	-	6.25	6.25	12.5	12.5	6.25	-	6.25	6.25	12.5	c
47	12.5	-	25	-	-	-	12.5	-	12.5	6.25	c
48	-	6.25	6.25	6.25	-	25	25	12.5	-	25	c

49	-	12.5	12.5	25	-	12.5	12.5	12.5	-	25	c
50	25	6.25	6.25	12.5	25	6.25	6.25	12.5	6.25	25	c
51	25	12.5	-	-	-	6.25	25	12.5	-	-	c
52	6.25	-	25	-	25	-	-	-	-	-	c
53	-	25	12.5	-	-	-	-	-	6.25	25	d
54	6.25	25	-	-	25	25	-	25	-	-	d
55	25	-	-	6.25	-	25	-	-	6.25	25	d
56	-	12.5	-	-	12.5	-	-	12.5	6.25	-	e
57	-	12.5	25	6.25	-	25	-	-	-	6.25	e
58	12.5	6.25	-	-	-	12.5	-	-	-	-	e
59	-	-	12.5	12.5	-	12.5	-	-	25	-	e
60	25	12.5	25	-	-	-	6.25	-	25	-	e
61	6.25	25	12.5	-	-	6.25	-	-	-	25	d
62	-	-	6.25	-	-	6.25	6.25	-	-	12.5	d
63	6.25	25	6.25	-	-	25	6.25	25	-	12.5	d
64	-	-	-	25	-	-	6.25	25	-	-	d
65	25	25	-	-	25	-	-	-	25	-	d
66	6.25	-	-	-	25	-	-	-	-	-	d
67	-	-	6.25	-	-	-	-	-	-	-	d
Std-1	50	12.5	50	12.5	25	-	-	-	-	-	e,d
Std-2	-	-	-	-	-	25	25	50	50	25	a,d,e
68	12.5	6.25	-	12.5	-	12.5	-	-	12.5	6.25	f
69	25	12.5	25	-	-	25	12.5	25	-	-	f
70	-	12.5	25	12.5	25	12.5	25	25	-	25	f
71	12.5	12.5	25	-	-	25	12.5	12.5	-	12.5	f
72	12.5	12.5	25	25	-	25	-	-	25	-	f
73	12.5	6.25	25	12.5	25	12.5	12.5	25	-	25	f
74	25	6.25	25	-	-	12.5	25	25	12.5	-	f
75	25	6.25	-	25	-	25	-	-	25	-	f
76	8	-	nr	nr	16	8	nr	-	nr	-	g
77	8	-	nr	nr	16	-	nr	16	nr	8	g
78	4	8	nr	nr	4	4	nr	16	nr	8	g
79	4	8	nr	nr	8	8	nr	-	nr	4	g
80	4	8	nr	nr	8	-	nr	16	nr	4	g
81	8	-	nr	nr	-	-	nr	-	nr	-	g
82	2	8	nr	nr	2	8	nr	16	nr	16	g
83	4	16	nr	nr	8	16	nr	16	nr	8	g
84	4	16	nr	nr	16	4	nr	2	nr	2	g
85	16	-	nr	nr	8	-	nr	-	nr	16	g
86	25	12.5	nr	nr	nr	6.25	nr	nr	25	25	h
87	25	12.5	nr	nr	nr	25	nr	nr	25	12.5	h
Std-3	4	16	-	-	2	-	-	-	-	-	g
Std-4	-	-	-	-	-	1	-	4	-	2	g

Sa:S. aureus; Bs:B. subtils; St: S. tyhpi; Ec: E. coli; Kp: K. pneumonia; Ca: C. albicans; Ro:R. oryzae; An: A. niger; Af: A. flavus; Cn: C neoformans; Pa: P aeruginosa; [a][18]; [b][8]; [c][28]; [d][24]; [e][25]; [f][20]; [h][26]; C5: Candida-51 (isolate strain); nr-not reported, -: indicates reported activity at a concentration higher than 25 µg/mL, or 20 µg/mL for MIC_{90}; [g]Parthiban and co-workers [7] reported MIC_{90}, the lowest concentration that inhibit 90% of pathogen growth; Std-1: Streptomycin; Std-2: Amphotericin B; Std-3-Gentamycin; Std-4: Fluconazole.

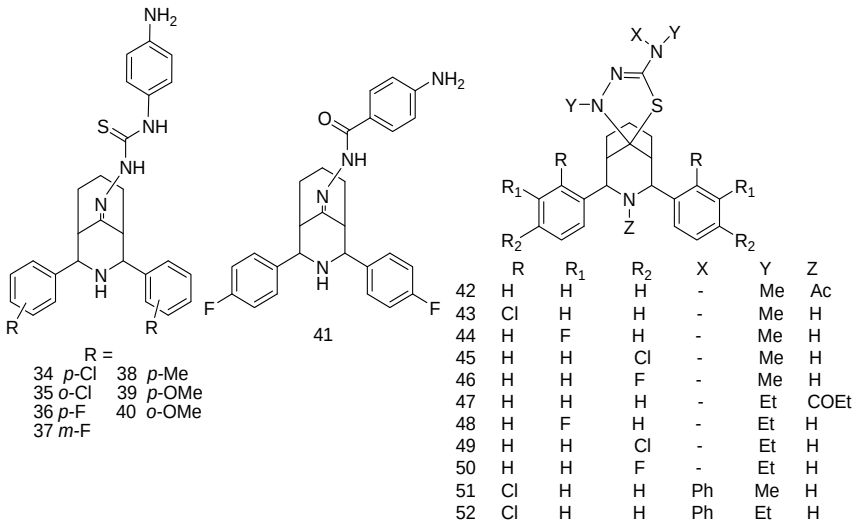
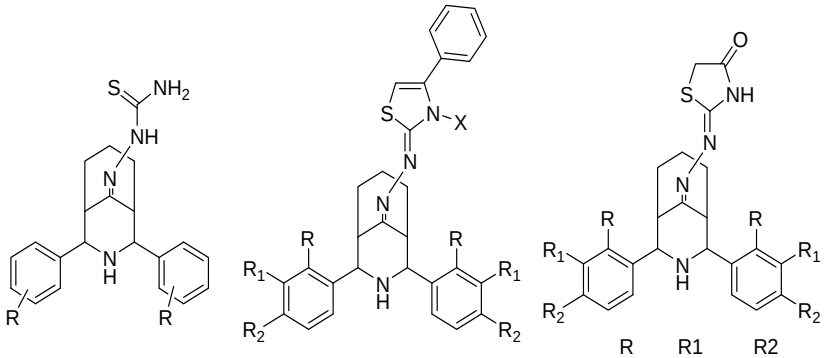


Figure 4

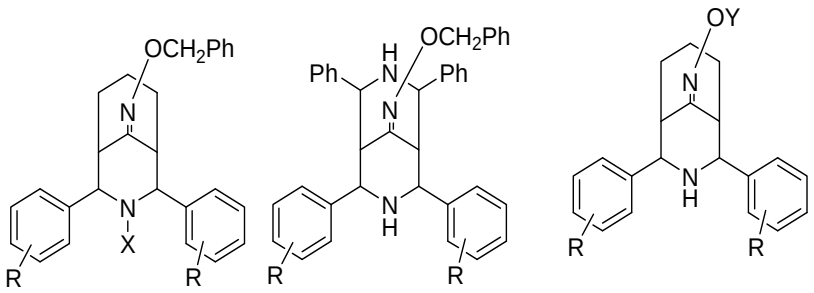


	R =
53	*p*-F
54	*m*-F
55	*p*-Cl

	R	R1	R2	X
56	H	H	F	H
57	Cl	H	H	H
58	H	H	F	Ph
59	H	F	H	Ph
60	H	H	Cl	Ph

	R	R1	R2
61	H	H	F
62	H	F	H
63	H	H	Cl
64	Cl	H	H
65	H	H	Me
66	H	H	OMe
67	H	OMe	H

Figure 5

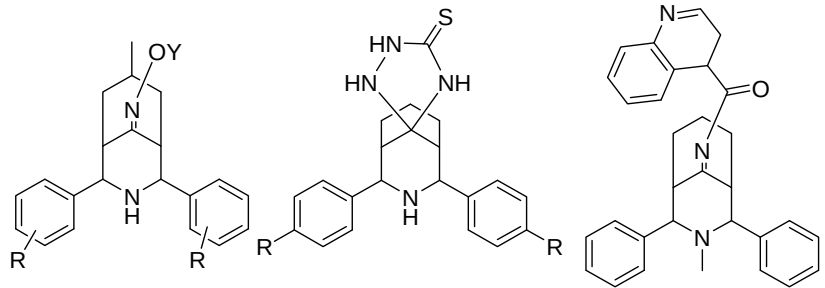


	R	X
68	*o*-Cl	H
69	*p*-Cl	H
70	H	Me
71	*p*-F	Me

	R
72	*m*-F
73	*p*-F
74	*p*-Cl
75	*p*-Me

	R	Y
76	*o*-F	H
77	*o*-Cl	H
78	*o*-F	Me
79	*p*-F	Me
80	*o*-Cl	Me

Figure 6



	R	Y
81	*p*-F	H
82	*o*-F	Me
83	*p*-F	Me
84	*o*-Cl	Me
85	*p*-Cl	Me

	R
86	*p*-Me
87	*p*-OMe

88

Figure 7

8. References

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