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Antimicrobial and antioxidant activities of piperidine derivatives

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Six novel piperidine derivatives, compounds 5 to 10, have been synthesized and their antimicrobial and anti-oxidant activities evaluated using agar disc diffusion (antimicrobial) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging capacity (antioxidant). Compound 9 revealed the least antibacterial activity. Compound 6 exhibited the strongest inhibitory activity and the best minimum inhibitory concentration (MIC) results against the seven bacteria tested in comparison to the other piperidine derivatives (5, 7, 8, 9, and 10). All six piperidine compounds displayed no activity against fungal species, *Fusarium verticilliodes, Candida utilus* and *Penicillium digitatium*. Compounds 7 and 8 revealed no activity against all seven fungi tested. Compounds 5, 6, 9, and 10 revealed varying degree of inhibition against *Aspergillus niger*, *Aspergillus flavus, Saccharomyces cerevisiae* and *Candida albicans*. Compound 8 demonstrated the highest scavenging capacity of 78% at 1000 µg/ml and compound 6 demonstrated the least percentage of scavenging potential of 49% at 1000 µg/ml. All piperidine derivatives tested, revealed antioxidant potentials greater than 49% at 1 mg/ml as compared to the control Rutin, which displayed 97% scavenging capacity at the same concentration. All piperidine derivatives revealed varying degree of antimicrobial and antioxidant activities.

Key words: 1,2,5,6-Tetrahydropyridine (THP), piperidine derivatives, antibacterial, antifungal, antioxidant.

INTRODUCTION

Antibiotic resistance and re-emerging diseases are known to cause major medical challenges in most healthcare systems (Hogberg et al., 2010). Resistance and multidrug-resistant pathogens are spreading with extraordinary speed, globally (Hogberg et al., 2010) leading to increased mortality rates amongst patients infected (Freire-Moran et al., 2011). Microorganisms are known to frequently form a resistance against pharmaceutically available drugs (Padmavathi et al., 2005). These drugs frequently lack selectivity and ability as well as unfavorable side effects (Padmavathi et al., 2005). The key to efficient and effective treatment of emerging diseases lies in the early stages of identification, diagnosis and treatment of these infections.

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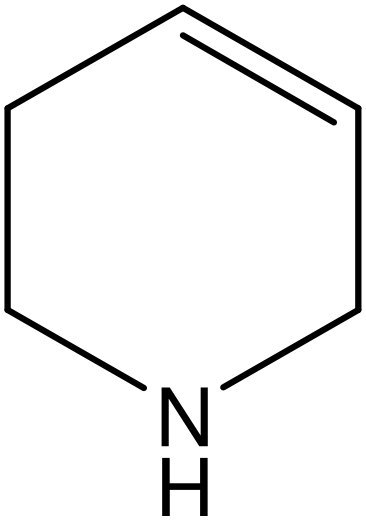


Figure 1. Tetrahydropyridine core of piperidine derivatives. Source: Maxime (2004).

Thus, there is a constant need for novel therapeutic agents. Tetrahydropyridine (THP) (Figure 1) derivatives have recently generated intense attention in the field of organic, bio-molecular chemistry and biotechnology due to their useful biological properties (Blackburne et al., 1975).

THP (Figure 1) is the core of piperidine derivatives and is found in numerous natural and synthetic pharmaceuticals and a wide variety of biologically active compounds (Mishra and Ghosh, 2011; Sumati Anthal et al., 2013).

Piperidine scaffold has found beneficial roles in numerous pharmaceutical drugs that are currently available in the market (Perumal et al., 2014, Das and Brahmachari, 2013, Sumati Anthal et al., 2013). Piperidine derivatives can be isolated from plant materials and synthesized using one or more of the many chemical reactions that have been established for the synthesis of piperidine derivatives (Anthal et al., 2013). The synthesis of piperidines and their derivatives have attracted the attention of organic and medicinal chemists, as these are commonly used in numerous natural products, pharmaceuticals and agrochemicals (Pizzuti et al., 2008). Alogliptin (1), ritalin (2), and risperidone (3) are pharmaceutically available drugs containing the piperidine nucleus that are utilized for the treatment of diabetes, improved concentration in children, and reduce schizophrenia. The drug CP-690550 (4) also known as Janus kinase 3 (JAK3), inhibits autoimmune diseases and used in transplant patients (Aeluri et al., 2012).

Derivatives containing the tetrahydropyridine nucleus (Figure 1) demonstrate a comprehensive variety of pharmacological activities including antimicrobial (Zhou et al., 2007), antimalarial (Safaei-Ghomi and Ziarati, 2013), anticonvulsant, anti-parasitic, cytotoxic, anti-inflammatory, pesticidal and anti-HIV-1 properties (Prachayasittikul et al., 2009; Sumati et al., 2013). The nucleus is present in various therapeutic agents including numerous antihistamines, antiseptics, anti-arrhythmic, anti-rheumatic and many other pharmaceutical and natural products (Ravindernath and Reddy, 2013).

The aim of this study was to synthesize six piperidine derivatives (5 to 10) (Figure 3) and evaluate their antimicrobial and antioxidant activities using agar disk diffusion assay and DPPH scavenging capacity technique, respectively.

MATERIALS AND METHODS

General procedure

All chemicals used were obtained from Sigma and Merck chemical companies and used without further purification. Thin layered chromatography (TLC) was performed on Merck 60F-254 silica gel plates with ethyl acetate and *n*-hexane (3:2) as the solvent system and visualized using ultra violet (UV) light. Melting points were determined by Thiele apparatus and uncorrected. Suitable crystals for x-ray analysis were grown from a mixture of ACN: THF (v/v; 1:1) solvent by slow evaporation at room temperature.

Synthesis of piperidine derivatives (5 to 10)

The piperidine derivatives were synthesized as follows (Venugopala et al., 2012) (Figure 4): Aniline (0.01 mol), aldehyde (0.01 mol), *β* keto-ester (0.005 mmol), $ZnCl_2$ (0.01 mol) and ethanol (10 ml) was added to a 50 ml round bottom flask. This mixture was stirred at room temperature for 7 to 9 h. Reactions were monitored by TLC. The solid precipitate obtained was filtered by vacuum and washed with aqueous ethanol to obtain a crude product. Formation of the compounds were confirmed by liquid chromatography-mass spectrometry (LC-MS), an Agilent Technology 1200 series instrument was used.

Biological screening

The six piperidine derivatives were screened for anti-bacterial, anti-fungal (Choi et al., 2002) and anti-oxidant (Premalatha et al., 2013) activities. Each compound was tested in triplicate.

Antibacterial activity

The antibacterial activity and the minimum inhibitory concentration (MIC) of the compounds were carried out using agar disc diffusion (Cos et al., 2006; Abate et al., 1998) against bacterial strains which were obtained from the stock collection center at the Durban University of Technology which is based at the Department of Biotechnology and Food Technology. The bacterial strains used in this study were, *Bacillus cereus, Bacillus coagulans*, *Bacillus polymixa, Bacillus polymixa, Escherichia coli, Klebsiella pneumoniae, Micrococcus luteus, Staphylococcus aureus,*

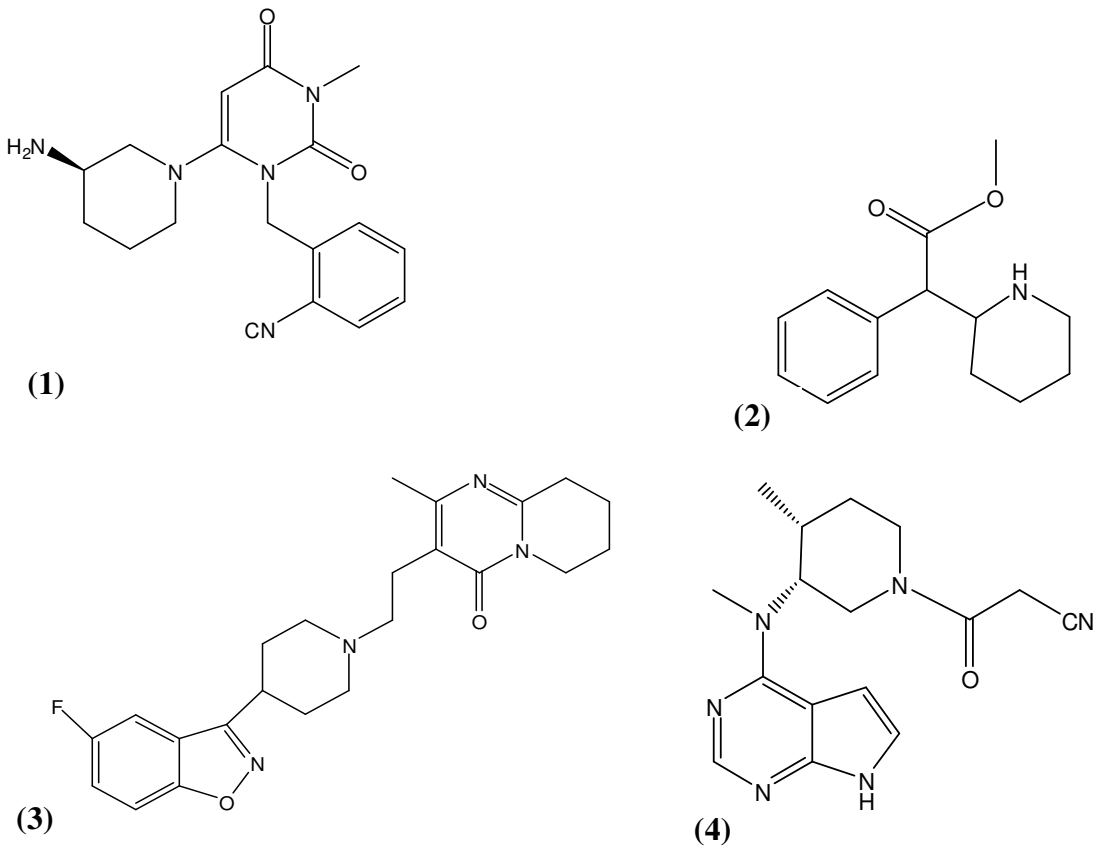


Figure 2. Pharmaceutically available drugs containing the piperidine core structure: Alogliptin (1), Ritalin (2), Risperidone (3), and CP-690550 (4). Source: Das and Brahmachari (2013).

Streptococcus faecalis and Serratia marcescens. Piperidine derivatives were dissolved in dimethyl sulfoxide (DMSO) and tested at the following concentrations, 6 mg/ml, 3, 1.5, 0.75, 0.375, 0.1875, 0.0093 and 0.0045 mg/ml. The antibacterial activity of the study compounds was determined by measuring the diameter of clearing around the disks in mm (Tables 2 and 3).

Antifungal activity

The antifungal assay was carried out using seven fungal cultures of which four were yeast, *A. flavus, A. niger, P. digitatium* and *F. verticilloides* and three moulds, *C. albicans*, *C. utilis* and *Saccharomyces cerevisiae.* The fungal strains were inoculated onto Sabouraud dextrose agar (SDA) (Biolab, Merck, South Africa). Piperidine derivatives were tested at 3 mg/ml. 100% DMSO (10 µl) was used as the negative control whilst Amphotericin B (10 µl at 3 mg/ml) (Sigma) was used as a positive control. The antifungal activity of the study compounds were determined by measuring the diameter of clearing around the disks in mm (Table 4).

Antioxidant activity

The anti-oxidative properties of the six piperidine analogues were tested using the 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) photometric assay described by (Choi et al., 2002). Stock solutions (2000 µg/ml) of piperidine analogues were prepared in DMSO and diluted to final concentrations of 1000, 800, 600, 400, 200 and 0 µg/ml. Absorbance values were measured in a Varian Cary 1E UV-visible spectrophotometer at 518 nm against the blank. The percentage of antioxidant activity (Figure 5) with different concentrations of the test compounds were calculated and compared with Quercetin-3-rutinoside a comparative standard. Each assay were carried out in triplicate and results achieved are expressed as IC_{50} values (Table 4) (Choi et al., 2002) (the concentration of the test is required to scavenge 50% free radicals).

RESULTS AND DISCUSION

Some physicochemical characteristics of the synthesized six piperidine derivatives (**5** - **10**) are depicted in Table 1. The current study focuses on the pharmacological activities namely, antimicrobial and anti-oxidant activity of six novel piperidine derivatives (**5-10**) (Table 5).

Antimicrobial

The *in vitro* antibacterial test conducted, revealed that

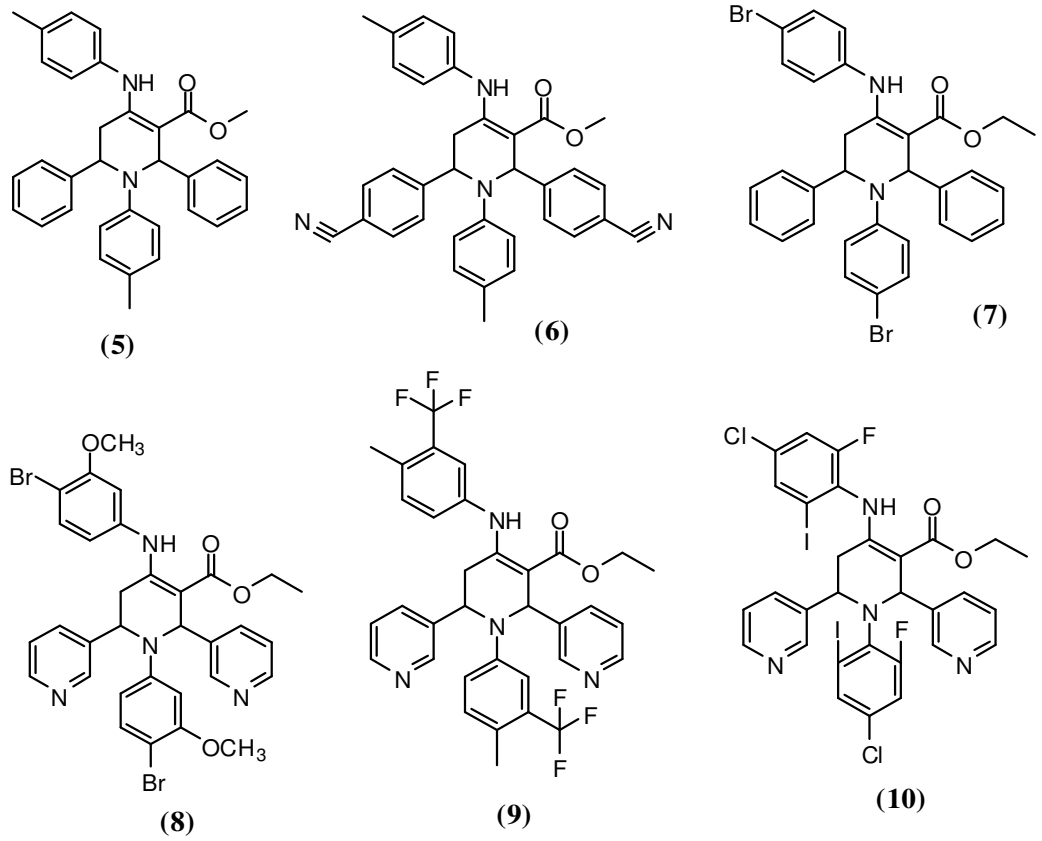


Figure 3. Chemical structures of the six novel piperidine derivatives (**5** - **10**).

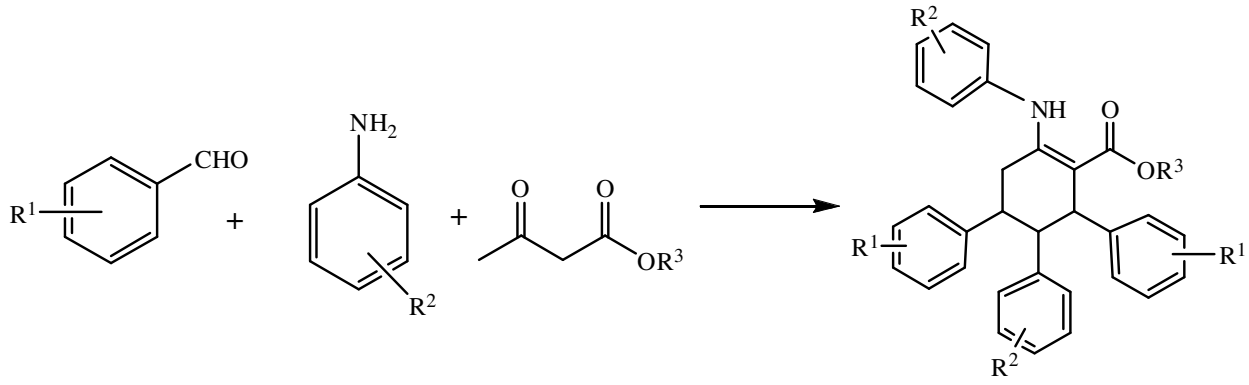


Figure 4. General synthesis of piperidine derivatives (5 – 10).

compounds 5-10 (Table 1) exhibited potent inhibition activity towards seven of the ten bacteria tested. All results collected are expressed as mean ± standard deviation values with antibacterial and antifungal activities results displayed as zones of inhibition (Table 2). It is more attractive to hypothesize that the observed results appear to be related to the nature of the substitutions on the piperidine moiety, with varying degree of potent inhibition activity towards *B. cereus, B. subtilus*, *S. aureus, E. coli, K. pneumoniae, M. luteus* and

Table 1. Physicochemical characteristics and physical state of 1,2,5,6-tetrahydropyridine compounds.

Compound code	Compound IUPAC name	Molecular formula	Molar mass	Yield (%)[a, b]	Melting point (°C)		cLog*P*[c]
					Reported	Observed	
5	Methyl 2,6-diphenyl-1-p-tolyl-4-(p-tolylamino)-1,2,5,6-tetra hydropyridine-3-carboxylate	$C_{33}H_{32}N_2O_2$	488	80	220-222	220	8.4666
6	Methyl 2,6-bis(4-cyanophenyl)-1-p-tolyl-4-(p-tolylamino)-1,2,5,6-tetra hydropyridine-3-carboxylate	$C_{35}H_{30}N_4O_2$	538	75	214	215	7.3326
7	Ethyl 1-(4-bromophenyl)-4-(4-bromophenylamino)-2,6-diphenyl-1,2,5,6-tetra hydropyridine-3-carboxylate	$C_{32}H_{28}Br_2N_2O_2$	632	85	NR	185	10.1968
8	Ethyl 1-(4-bromo-3-methoxyphenyl)-4-(4-bromo-3-methoxyphenylamino)-2,6-di(pyridin-3-yl)-1,2,5,6-tetra hydropyridine-3-carboxylate	$C_{32}H_{30}Br_2N_4O_4$	692	81	NR	200	6.7653
9	Ethyl 1-(4-methyl-3-(trifluoromethyl)phenyl)-4-(4-methyl-3-(trifluoromethyl) phenylamino)-2,6-di(pyridin-3-yl)-1,2,5,6-tetrahydro pyridine-3-carboxylate	$C_{34}H_{30}F_6N_4O_2$	640	79	NR	208	8.5957
10	Ethyl 1-(4-chloro-2-fluoro-6-iodophenyl)-4-(4-chloro-2-fluoro-6-iodophenylamino)-2,6-di(pyridin-3-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate	$C_{30}H_{22}Cl_2F_2I_2N_4O_2$	831	65	NR	226	9.6583

P. aurenginosa, with exceptions to *Streptococcus faecalis, Serratia marcescens,* and *Bacillus polymixa*. Piperidine derivative (compound 8) revealed the least antibacterial activity (5 mm) inhibition zones towards *B. subtilus, S. aureus* and *P. aurenginosa.* Compound 6 exhibited the strongest inhibitory activity (≥ 6 mm zones of inhibition), revealing great inhibition effects towards *B. cereus, E. coli, S. aureus, B. subtilus, P. aurenginosa, Kl. pneumoniae* and *M. luteus*. Compound 6 also exhibited the best MIC results of 0.75 mg/ml against *B. subtilus* and 1.5 mg/ml against *B. cereus, E. coli, S. aureus, P. aurenginosa, Kl. pneumoniae and M. luteus.* Compound 5 presented an MIC of 1.5 mg/ml against *E. coli, M. luteus, S. aureus, B. cereus* and *B. subtilus* while compound 7 generated an MIC of 1.5 mg/ml against *E. coli, B. cereus, S. aureus and B. subtilus*. Compound 8 revealed an MIC of 1.5 mg/ml towards *B. subtilus, S. aureus* and *M. luteus*. Compound 9 produced an MIC of 1.5 mg/ml against *E. coli*, *M. luteus, S. aureus, B. subtilus, P. aeruginosa* and *B. cereus.* Finally compound 10 displayed an MIC of 1.5 mg/mL against *B. cereus, M. luteus, S. aureus, B. subtilus, E. coli and P. aeruginosa.*

Piperidine derivatives possessing benzaldehyde (5 and 7), 4-cyano phenyl (6), pyridine (8, 9 and 10) groups as substitutions on C2 and C6 of the piperidne ring, as well as methyl or ethyl group on C3 displayed moderate inhibition activity. Both the electron donating as well as electron withdrawing groups present as substitutions on the piperidine ring enhanced the antibacterial activity. Ravindernath and Reddy (2013) revealed that piperidine derivatives containing hydroxy, methyl, and nitro substitutions on the phenyl ring revealed significant inhibition against the bacterial species tested resulting in tremendous antibacterial potential. This could be a reason for 6 to exhibit the greatest antibacterial activity in comparison to 5-10. Piperidine derivatives containing a flouro group as a substitution on the piperidine nucleus demonstrates pronounced antibacterial (Haider et al., 2014). Compounds 7 and 8 exhibited low

Table 2. Antimicrobial activities of the six novel piperidine derivatives at 3 mg/ml.

Micro-organism	Average Zones of inhibition (mm) [a, b]						
	5	6	7	8	9	10	Control
Bacteria							
B. cereus	5	6	5	4	5	5	11
E. coli	5	6	5	3	5	5	11
Kl. pneumoniae	n/a	5	4	2	4	4	11
S. aureus	5	6	5	5	5	5	11
S. marcescens	n/a	n/a	n/a	n/a	n/a	n/a	11
B. polymixa	n/a	n/a	n/a	n/a	n/a	n/a	11
B. subtilus	5	7	5	3	6	5	11
M. luteus	6	6	3	5	5	5	11
P. aurenginosa	n/a	6	1	5	5.5	6	11
S. facealis	n/a	n/a	n/a	n/a	n/a	n/a	11
Fungi							
A. niger	5	5	n/a	n/a	5	5	7.5
A. flavus	5	5.5	n/a	n/a	n/a	n/a	7.5
F. verticilliodes	n/a	n/a	n/a	n/a	n/a	n/a	7.5
P. digitatium	n/a	n/a	n/a	n/a	n/a	n/a	7.5
C. utilis	n/a	n/a	n/a	n/a	n/a	n/a	7.5
C. albicans	5	5	n/a	n/a	6	6	7.5
S. cerevisiae	2	2	n/a	n/a	5	5	7.5

Data represented as mean ± standard derivation, Number of sample (n=3), n/a – (No activity), [a] Negative control (DMSO) – No activity, [b] Concentration 3 mg/ml.

Table 3. Minimum inhibition concentration (MIC) of the six novel piperidine derivatives using broth dilution technique.

Bacterial species	Minimum Inhibition Concentration (mg/ml) [a]					
	5	6	7	8	9	10
B. cereus	1.5	1.5	1.5	n/a	1.5	1.5
E. coli	1.5	1.5	1.5	n/a	1.5	1.5
Kl. pneumoniae	n/a	1.5	n/a	n/a	n/a	n/a
S. aureus	1.5	1.5	1.5	1.5	1.5	1.5
B. subtilus	1.5	0.75	1.5	1.5	1.5	1.5
M. luteus	1.5	1.5	n/a	1.5	1.5	1.5
P. aurenginosa	n/a	1.5	n/a	n/a	1.5	1.5

Data represented as mean values ± standard derivation, Number of sample (n=3), n/a (No activity), [a] Negative control (DMSO) – No activity.

inhibitory activity which could have developed by the substitution of 4-bromo group on NH-substitution on C4 of the piperidine ring.

The *in vitro* antifungal results of 5-10 are observed in Table 2. Compounds 5-10 exhibited no inhibitory activity towards *C. utilis*, *P. digitatium* and *F. verticilliodes.* Compounds 7 and 8 did not exhibit any inhibitory potential towards the fungi and this could have resulted from the addition of 4-bromo which is attached to an amino (NH) group on C6 of the piperidne ring. 5, 6, 9 and 10 displayed varying degree of inhibition towards *C. albicans*, *S. cerevisiae*, *A. flavus* and *A. niger.* Compound 5 exhibited moderate inhibitory (5 mm) towards *A. niger, A. flavus, S. cerevisiae* and *C. albicans*. This could have stemmed from the ethyl or methyl group being substituted to C3 of the piperidine ring which is known to increase

Table 4. Average % of DPPH free radical scavenging capacity obtainable by six novel piperidine derivatives (5-10) at 0, 200, 400, 600, 800 and 1000 µg/ml) concentrations.

Concentration (µg/ml)	Compound code						
	RUTIN	**5**	**6**	**7**	**8**	**9**	**10**
0	0±0	0±0.01	0±0.02	0±0.01	0±0	0±0.04	0±0.01
200	22±0	7±0.01	13±0.02	22±0.02	25±0.01	19±0	15±0.01
400	48±0	29±0	26±0.01	36±0	48±0	38±0	35±0.01
600	77±0	35±0.01	33±0	47±0	55±0	48±0	51±0
800	85±0	49±0	41±0	53±0	66±0.01	56±0	59±0
1000	97±0	58±0.01	49±0	61±0	78±0	67±0	70±0
p. value	0.0003***	0.0002***	0.0001***	0.0001***	0.0009***	0.0004***	0.0002***
IC_{50} value	464.68	838.93	959.69	730.99	584.8	689.66	667.56

Data represented Data represented as mean ± standard derivation, (Number of samples n=3). Negative control (DMSO) = 0. All values are significant with p value (two tailed)***= $p < 0.01$.

Table 5. Summary of the pharmacological activities exhibited by 5-10.

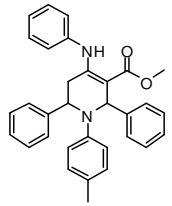
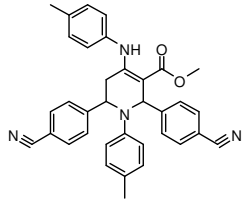
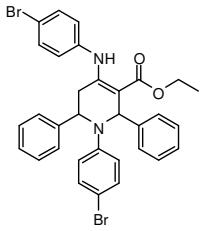
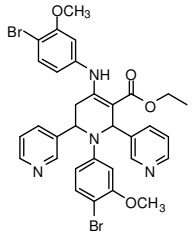
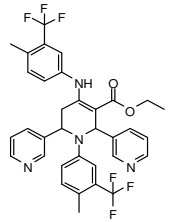
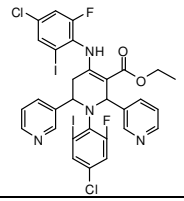
Compound	Structure	Antibacterial	Antifungal	Antioxidant
5		*B. cereus* (++), *E. coli* (++), *S. aureus* (++), *B. subtilus* (++), *M. luteus* (++)	*A. niger* (+), *A. flauvs* (+), *C. albican* (+)	838.93 at 1000 µg/ml
6		*B. cereus* (++), *E. coli* (++), *Kl. pneumonia* (++), *S. aureus* (++), *B. subtilus* (+++), *M. luteus* (++), *P. aurenginosa* (++)	*A. niger* (+), *A. flauvs* (+), *C. albican* (+)	959.69 at 1000 µg/ml

Table 5. Contd.

7		*B. cereus* (++), *E. coli* (++), *S. aureus* (++), *B. subtilus* (++), *Kl. pneumonia* (++)	-	730.99 at 1000 µg/ml
8		*S. aureus* (++), *M. luteus* (++), *P. aurenginosa* (++)	-	584.80 at 1000 µg/ml
9		*B. cereus* (++), *E. coli* (++), *S. aureus* (++), *B. subtilus* (++), *M. luteus* (++), *P. aurenginosa* (++)	*A. niger* (+), *S. cerevisiae* (+), C. *albicans* (+)	689.66 at 1000 µg/ml
10		*B. cereus* (++), *E. coli* (++), *S. aureus* (++), *B. subtilus* (+++), *M. luteus* (++), *P. aurenginosa* (++)	*A. niger* (+), *S. cerevisiae* (+), C. *albicans* (+)	667.56 at 1000 µg/ml

Antimicrobial IC_{50} represented as; 3 mg/ml- +, 1.5 mg/ml- ++, 0.75 mg/ml- +++.

antifungal potency (Premalatha et al., 2013). 6 displayed pronounced inhibition activity (≥ 5 mm) towards *A. niger, A. flavus, S cerevisiae and C. albicans.* This may have developed from the electron donating pyridine group on the C2 and C6 situated on the piperidine ring. 5 and 6 have

demonstrated superior activity in comparison to compounds 7-10. Rafiq (2013) proves that fluoro as a substitution on phenyl group of a piperidine ring similar to 9 and 10 which has found to exhibit ≥5 mm inhibition activity towards *A. niger and C. albicans*.

Antioxidant

Piperidine derivative 8 demonstrated the highest scavenging capacity of 78% at 1000 µg/ml while 6 demonstrated the least scavenging potential of 49% at 1000 µg/ml. This good activity of **8** may have resulted from the presence of a methoxy group as a substation on C2 and C6 of the piperidine ring and the low activity displayed by 6 may have stemmed from the substitution of 4-cyanopheyl on C2 and C6 of the piperidine ring structure. Rutin, exhibited an antioxidant potential of 99% at 1000 µg/mL which is higher than 5-10. The IC_{50} values of all piperidine derivatives, 5-10 ranged between 584.8 - 959.69 µg/mL antioxidant activities. Test compounds containing specific substitutions groups, namely, Benzaldehyde (5 and 7), 4-cyano phenyl (6), 4-Methyl-3-trifluoromethylphenyl (9) and 4-chloro-2-flouro-4-iodophenyl (10) which is substituted on C2 and C6 of the piperidine ring as resulted in different levels of DPPH free radicals activity. The substitution of hydroxyl, methoxy, nitro and alkyl group on the piperidine ring revealed good antioxidant activities (Ravindernath and Reddy, 2013).

Conclusion

This study concludes that all 1,2,5,6-tetrahydropyridine compounds (5-10) exhibit varying degree of inhibition against bacterial and fungal species (Table 5). The antioxidant activities are directly proportional to the percentage of scavenging capacity and inversely proportional to the IC_{50} value. The piperidine nucleus plays an important role in inhibition activity of 1,2,5,6-tetrahydropyridine and therefore it is highly significant in influencing the biological activities when present. Future work should involve minor alteration to the structural side chains of the compound to allow the compound to change the genetic make-up of the microorganisms resulting in these compounds displaying antimicrobial (Haider et al., 2014) and antioxidant characteristic.

Conflict of Interest

The authors have not declared any conflict of interest.

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