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Synthesis and spermicidal activity of substituted (E)-3-(aryl/heteroaryl)-1-phenylprop-2-en-1-ones

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ABSTRACT

In the search of new and efficient spermicidal agents, substituted chalcones or 1,3-diaryl-2-propen-1-ones possessing acrylophenone moiety in their structural framework, have been synthesized by condensing aryl ketones with aromatic aldehydes under basic conditions via Claisen-Schmidt condensation. The synthesized compounds were characterized by elemental analysis, ^{1}H and ^{13}C NMR. The prepared compounds have been screened for their spermicidal activity against human spermatozoa. Bio-evaluation studies of these molecules revealed that compound JS16 was the most potent spermicide among the series with MEC of 0.05 %. The present communication describes syntheses, bio-evaluation and structure-related spemicidal activity of (E)-3-(substitutedaryl/heteroaryl)-1-substitutedphenylprop-2-en-1-ones.

Key words: Chalcone, acrylophenone, spermicidal, acrosome

INTRODUCTION

Good reproductive health is the basis for intimate relationship, happy family and healthy children, which ensures that every child is wanted, every birth is safe, and every person is free of sexually transmitted infection (STI) and human immunodeficiency virus (HIV). According to an estimate, 40% of all pregnancies that occurred worldwide in 2008 were unintended, which strongly indicates that the available methods of contraception are insufficient to cater the unmet need of millions of couples and therefore, need for developing newer, cost-effective, safe and self-administrable spermicides has become an urgent global priority [1].

Currently all commercially available spermicidal preparations are mostly based on Nonoxynol-9 (N-9, mixture of oligomers) a detergent ingredient with potent spermicidal properties. due to its surfactant-type of action it cause irritation to the vagina and rectum and even damages the cervicovaginal epithelium because of its membrane-disruptive properties, causing an acute inflammatory tissue response, altered vaginal microflora and increase the chance of HIV transmission [2-7]. The other surfactants like octoxynol-9, menfegol (TS-88) and benzalkonium chloride that have been used as spermicides, also non-specifically disrupt cell membranes and are, therefore, cytotoxic to a wide range of cell types including Lactobacilli, which facilitate the maintenance of an optimal environment in the vagina [8,9]. These limitations of using spermicidal surfactants prompted the search for developing user-controlled, non-detergent, topical vaginal spermicidal microbicides that are more effective as well as safer for providing contraception with prophylaxis against STDs. Such agents can effectively alleviate the global crisis of unwanted pregnancies and AIDS [10-12].

1,3-diaryl-2-propen-1-ones or chalcones is an important class of naturally occurring secondary metabolites of interest had attracted the synthetic chemists for their diverse array of pharmacological properties [13]. Chemically, they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α, β unsaturated carbonyl system. The presence of a reactive α, β unsaturated keto function in chalcones is found to be responsible for their varied biological activities [14]. In recent years, variety of chalcones have been reviewed for their anti-bacterial, antiulcer, antifungal, antioxidant, vasodilatory, antimitotic, antimalarial, antileshmanial. Number of chalcone derivatives, have also been found to inhibit several important enzymes in cellular systems, including xanthine oxidase, aldose reductase, epoxide hydrolase, protein tyrosine kinase and quinone reductase. Appreciation of these findings motivated us to synthesize a series of chalcones as a potential template for spermicidal agents [15-20].

Among the pharmacophores imparting spermicidal activity acrylophenones have been reported as potent, non-detergent spermicides against human spermatozoa [5,6]. In view of well versed spermicidal activity of acrylophenone class of compounds, 1,3-diaryl-2-propen-1-ones possessing acrylophenone moiety in their structural framework, need to be explored for their spermicidal potential (Figure 1).

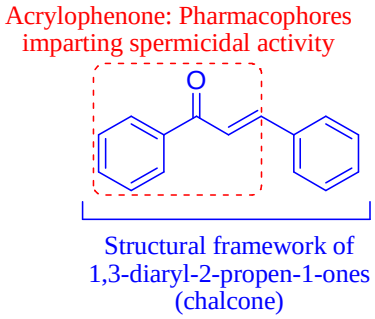


Figure 1: Design strategy

MATERIALS AND METHODS

The reagents were purchased from Sigma Aldrich, Merck, CDH, Loba chem., Spectro chem., India and used without further purification. All yields refer to isolated products after purification. Melting points were recorded on Decibel Digital melting point apparatus in open glass capillary tubes and are uncorrected. ^{1}H & ^{13}C NMR spectra were recorded on a Bruker Advance II 500 MHz instrument with $CDCl_3$ as solvent at 500 and 125 MHz, respectively. Chemical shifts were reported in δ (ppm) downfield from tetramethylsilane, and coupling constants (*J*) are expressed in hertz. Multiplicities are recorded as s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet). Thin layer chromatography (TLC) was done on pre-coated silica plates. Ethyl acetate and n-hexane mixture was used as eluent for the chromatographic purification of the compounds. Spots were visualized on exposure to UV light.

1.1. General procedure for synthesis of (E)-3-(substitutedaryl/heteroaryl)-1- substitutedphenylprop-2-en-1-ones (JS1-JS40).

Substituted aryl ketone (1 mmol) was taken in a flask (50 mL) and was dissolved in 10 mL methanol. Substituted aromatic aldehyde (1 mmol) was added to the solution followed by 10 % aqueous NaOH solution (2 mL), and the reaction mixture was kept in stirred condition at 15–20 ºC until completion of the reaction. Progress of the reaction was monitored by TLC (7:3, n-hexane : ethyl acetate). After the completion of the reaction, the reaction mixture was poured in ice cold water, filtered, solid was washed with water and dried in air to afford the crude product. The crude product was crystallized (EtOH) to get pure compound. The spectral data (elemental analysis, ^{1}H and ^{13}C NMR) for all the synthesized compounds is provided below:

1.1.1. *(E)-1,3-diphenylprop-2-en-1-one (JS1):* Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81 %. Found: C, 86.42; H, 5.67 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (1H, *d*, *J* = 16.0 Hz), 7.81 (2H, *d*, *J* = 8.4 Hz), 7.56 (1H, *d*, *J* = 16.0 Hz), 7.54 (1H, *m*), 7.45-7.50 (2H, *m*), 7.30 (2H, *d*, *J* = 7.8 Hz), 7.21-7.25 (2H, *m*), 7.14 (1H, *m*). ^{13}C NMR (125

MHz, $CDCl_3$): δ 189.71, 145.23, 137.91, 135.21, 134.61, 129.92, 129.90, 129.31, 129.30, 128.73, 128.71, 128.11, 126.43, 126.41, 121.12.

1.1.2. *(E)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (JS2):* Anal. Calcd for $C_{15}H_{11}FO$: C, 79.63; H, 4.90; F, 8.40 %. Found: C, 79.71; H, 4.68; F, 8.66 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, *d*, *J* = 10 Hz), 7.80 (1H, *d*, *J* = 20 Hz), 7.60-7.67 (3H, *m*), 7.47-7.55 (3H, *m*), 7.12-7.15 (2H, *m*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 116.05, 116.23, 121.80, 128.49, 128.66, 130.39, 131.14, 132.86, 138.14, 143.50, 163.07, 165.07, 190.31.

1.1.3. *(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (JS3):* Anal. Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Cl, 14.61 %. Found: C, 74.46; H, 4.67; Cl, 14.34 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.09 (2H, m), 8.00 (1H, *d*, *J* = 15 Hz), 7.87-7.92 (2H, m), 7.83 (1H, *d*, *J* = 10 Hz), 7.67 (1H, *d*, *J* = 15 Hz), 7.61-7.64 (1H, m), 7.54-7.57 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 122.23, 123.67, 126.78, 127.38, 127.81, 128.53, 128.65, 128.74, 130.66, 132.78, 133.38, 134.40, 138.31, 144.94, 190.05.

1.1.4. *(E)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (JS4):* Anal. Calcd for $C_{15}H_{11}BrO$: C, 62.74; H, 3.86; Br, 27.83 %. Found: C, 62.88; H, 4.11; Br, 28.05 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (2H, *d*, *J* = 6.3 Hz), 7.70 (1H, *d*, *J* = 15.3 Hz), 7.47-7.50 (8H, *m*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.72, 145.23, 137.89, 135.10, 134.64, 129.87, 129.81, 129.83, 128.62, 128.60, 128.23, 126.35, 126.33, 129.20, 121.33.

1.1.5. *(E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (JS5):* Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53 %. Found: C, 70.96; H, 4.57; N, 5.63 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-8.25 (2H, *m*), 7.76-8.01 (3H, *m*), 7.44-7.59 (6H, *m*). . ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.72, 145.33, 138.86, 134.13, 133.64, 129.77, 129.82, 129.84, 128.80, 128.52, 128.65, 128.23, 126.45, 126.43, 121.33.

1.1.6. *(E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (JS6):* Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92 %. Found: C, 80.37; H, 6.16 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, *d*, *J* = 5 Hz), 7.82 (1H, *d*, *J* = 15 Hz), 7.58-7.64 (3H, *m*), 7.51-7.54 (2H, m), 7.45 (1H, *d*, *J* = 15 Hz), 6.96 (2H, *d*, *J* = 5 Hz), 3.88 (3H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.43, 114.44, 119.81, 127.63, 128.43, 128.57, 130.24, 132.56, 138.53, 144.72, 161.69, 190.61.

1.1.7. *(E)-3-(3-chlorophenyl)-1-phenylprop-2-en-1-one (JS7):* Anal. Calcd for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Cl, 14.61%. Found: C, 74.37; H, 4.78; Cl, 14.23 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (1H, *d*, *J* = 7.8 Hz), 7.17 (1H, *m*), 7.19 (1H, *d*, *J* = 8.4 Hz), 7.31 (1H, *s*), 7.36 (1H, *d*, *J* = 15.6 Hz), 7.45 (2H, *m*), 7.54 (1H, *m*), 7.81 (2H, *d*, *J* = 7.4 Hz), 7.91 (1H, *d*, *J* = 15.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ δ 187.72, 142.20, 138.96, 136.23, 135.65, 129.67, 129.72, 129.74, 128.90, 128.72, 128.85, 126.23, 126.21, 126.40, 120.36.

1.1.8. *(E)-3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one (JS8):* Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92%. Found: C, 80.56; H, 6.23 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (3H, *s*), 6.72 (1H, *d*, *J* = 8.2 Hz), 6.77 (1H, *m*), 7.03 (1H, *m*), 7.19 (1H, *d*, *J* = 8.0 Hz), 7.39 (1H, *d*, *J* = 16.2 Hz), 7.44 (2H, *m*), 7.55 (1H, *m*), 7.80 (2H, *d*, *J* = 7.7 Hz), 8.17 (1H, *d*, *J* = 161.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.74, 157.69, 148.22, 136.89, 133.63, 129.89, 128.32, 128.52, 128.42, 127.20, 127.12, 121.42, 120.90, 114.28, 115.09, 56.30.

1.1.9. *(E)-3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one (JS9):* Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01 %. Found: C, 75.80; H, 6.28 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (2H, *d*, *J* = 5 Hz), 7.77 (1H, *d*, *J* = 15 Hz), 7.57-7.60 (1H, *m*), 7.49-7.52 (2H, *m*), 7.40 (1H, *d*, *J* = 15 Hz), 7.24 (1H, *d*, *J* = 10 Hz), 7.17 (1H, *s*), 6.90 7.24 (1H, *d*, *J* = 5 Hz), 3.96 (3H, *s*), 3.93 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.97, 56.00, 110.09, 111.13, 120.06, 123.20, 127.86, 128.43, 128.57, 132.57, 138.48, 145.02, 149.25, 151.45, 190.59.

1.1.10. *(E)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (JS10):* Anal. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96 %. Found: C, 72.73; H, 4.58; S, 15.26 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (2H, *d*, *J* = 10 Hz), 7.97 (1H, *d*, *J* = 15 Hz), 7.58-7.61 (1H, *m*), 7.50-7.53 (2H, *m*), 7.43 (1H, *d*, *J* = 5 Hz), 7.34-7.37 (2H, *m*), 7.10-7.11 (1H, *m*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.80, 128.38, 128.42, 128.64, 128.85, 132.09, 132.79, 137.21, 138.13, 140.40, 189.86.

1.1.11. *(E)-3-Phenyl-1-(1H-pyrrol-2-yl)prop-2-en-1-one (JS11):* Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10 %. Found: C, 79.38; H, 5.77; N, 7.11 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (1H, *dd*, *J* = 2.4 Hz and 3.8 Hz),

7.19 (1H, *d*, *J* = 15.0 Hz), 7.34 (5H, *m*), 7.45 (1H, *d*, *J* = 15.0 Hz, H-3), 7.76 (2H, *bs*), 10.65 (1H, *s*, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.81, 140.94, 133.12, 131.35, 130.21, 130.12, 127.98, 126.08, 125.90, 121.88, 111.43.

1.1.12. *(E)-3-(Phenyl)-1-(furan-2-yl)prop-2-en-1-one (JS12):* Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H. 5.09 %. Found: C, 79.03; H. 4.97 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (1H, *m*), 7.38 (1H, *dd*, *J* = 1.4 Hz and 3.2 Hz,), 7.45 (1H, *d*, J = 2.0 Hz,), 7.47 (2H, *m*), 7.48 (1H, *d*, *J* = 16.02 Hz,), 7.68 (3H, *m*), 7.92 (1H, *d*, *J* = 16.02 Hz,). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.00, 153.71, 146.54, 143.97, 134.73, 130.61, 128.95, 128.53, 121.18, 117.52, 112.55.

1.1.13. *(E)-1-phenyl-3-(pyridin-4-yl)prop-2-en-1-one (JS13):* Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69%. Found: C, 80.36; H, 5.30; N, 6.69 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (2H, *m*), 7.50 (1H, *m*), 7.51 (2H, *d*, *J* = 8.5 Hz), 7.56 (1H, *d*, *J* = 15.5 Hz), 7.80 (2H, *d*, *J* = 7.5 Hz), 7.88 (1H, *d*, *J* = 15.5 Hz), 8.71 (2H, *d*, *J* = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.69, 149.71, 149.78, 148.92, 146.52, 136.92, 133.65, 129.99, 128.91, 128.73, 128.32, 128.13, 120.71, 119.68.

1.1.14. *(E)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (JS14):* Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46 %. Found: C, 88.46; H, 5.13 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (7H, *m*), 7.82-7.94 (3H, *m*), 8.08 (2H, *d*, *J* = 18 Hz), 8.26 (1H, *d*, *J* = 8.1 Hz), 8.68 (1H, *d*, *J* = 15.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.74, 142.24, 137.89, 135.84, 133.99, 133.68, 132.11, 129.12, 129.10, 128.95, 128.77, 128.67, 127.32, 126.20, 125.95, 125.87, 124.10, 123.12, 121.42.

1.1.15. *(E)-3-(naphthalen-3-yl)-1-phenylprop-2-en-1-one (JS15):* Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46 %. Found: C, 88.46; H, 5.34 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.60 (5H, *m*), 7.65 (1H, *d*, *J* = 15.6 Hz), 7.79-7.89 (4H, *m*), 7.98 (1H, *d*, *J* = 15.6 Hz), 8.05-8.07 (3H, *m*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.76, 143.28, 137.97, 134.62, 133.61, 133.78, 132.98, 129.95, 129.25, 128.25, 128.10, 128.07, 127.99, 127.71, 126.45, 125.99, 124.95, 123.52, 120.99.

1.1.16. *(E)-3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one (JS16):* Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66 %. Found: C, 82.25; H, 5.00; N, 5.30 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.09 (1H, *s*), 9.09 (1H, *s*), 8.34-8.35 (1H, *m*), 8.13 (1H, *d*, *J* = 15 Hz), 8.04-8.09 (1H, *m*), 7.86 (1H, *d*, *J* = 5 Hz), 7.59-7.64 (1H, *m*), 7.53-7.56 (1H, *m*), 7.45-7.48 (2H, *m*), 7.33-7.39 (3H, *m*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 111.56, 111.98, 117.91, 120.71, 121.78, 121.96, 123.01, 123.54, 124.38, 124.45, 128.34, 128.55, 130.33, 132.28, 135.42, 138.97, 185.17.

1.1.17. *(E)-1-(4-methoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (JS17):* Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.12 %. Found: C, 68.62; H, 5.06; S, 13.24 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, *d*, *J* = 10 Hz), 7.95 (1H, *d*, *J* = 15 Hz), 7.42 (1H, *d*, *J* = 5 Hz), 7.35-7.38 (2H, *m*), 7.09-7.10 (1H, *m*), 6.99 (2H, *d*, *J* = 10 Hz), 3.90 (3H, *s*).^{13}C NMR (125 MHz, $CDCl_3$): δ 55.49, 113.85, 120.64, 128.29, 128.44, 130.71, 131.00, 131.74, 136.40, 140.58, 163.42, 188.07.

1.1.18. *(E)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (JS18):* Anal. Calcd for $C_{13}H_9BrOS$: C, 53.26; H, 3.09; Br, 27.25; S, 10.94 %. Found: C, 53.43; H, 2.92; Br, 27.56; S, 11.04 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (1H, *d*, *J* = 15 Hz), 7.88 (2H, *d*, *J* = 5 Hz), 7.66 (2H, *d*, *J* = 5 Hz), 7.45 (1H, *d*, *J* = 5 Hz), 7.39 (1H, *m*), 7.27-7.30 (1H, m), 7.10-7.12 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.10, 127.86, 128.43, 129.13, 129.92, 131.92, 132. 41, 136.84, 137.74, 140.19, 171.14, 188.70.

1.1.19. *(E)-1-(4-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (JS19):* Anal. Calcd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.92 %. Found: C, 67.99; H, 4.27; S, 14.11 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, *s*), 6.92 (2H, *d*, *J* = 7.9 Hz), 7.31 (1H, *m*), 7.55 (1H, *d*, *J* = 16.5 Hz), 7.62-7.66 (4H, *m*), 7.90 (1H, *d*, *J* = 16.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.68, 164.32, 137.82, 135.20, 130.99, 130.94, 130.70, 129.97, 128.19, 127.42, 127.10, 116.39, 115.99.

1.1.20. *(E)-1-(3,4-dimethoxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (JS20):* Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; S, 11.69 %. Found: C, 65.56; H, 5.34; S, 11.41 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (1H, *d*, *J* = 15.3 Hz), 7.61-7.68 (2H, *m*), 7.33-7.42 (3H, *m*), 7.07-7.10 (1H, *m*), 6.93 (1H, *d*, *J* = 8.4 Hz), 3.97 (6H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.69, 155.65, 150.29, 137.79, 134.23, 131.19, 129.99, 128.27, 127.39, 127. 09, 123.17, 115.09, 115.10, 56.19, 56.18.

1.1.21. *(E)-3-(4-Methoxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (JS21):* Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.11 %. Found: C, 74.03; H, 5.80; N, 6.15 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (3H, *s*), 6.35 (1H, *m*), 6.94 (2H, *d*, J = 8.76 Hz,), 7.06 (1H, *m*), 7.09 (1H, *m*), 7.25 (1H, *d*, *J* = 15.67 Hz), 7.60 (2H, *d*, *J* = 8.76 Hz,), 7.81 (1H, *d*, *J* = 15.67 Hz), 10.59 (1H, *s*, NH). ^{13}C NMR (125 MHz, CDCl3): δ 178.28, 163.48, 136.21, 133.49, 131.92, 128.56, 127.58, 125.98, 120.06, 118.89, 115.82, 55.71.

1.1.22. *(E)-3-(4-Bromophenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (JS22):* Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07 %. Found: C, 56.59; H, 3.68; N, 5.17 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.31 (1H, *m*), 7.21 (1H, *dd*, *J* = 1.47 and 0.56 Hz,), 7.42 (1H, *dd*, *J* = 1.11 and 2.6 Hz,), 7.64 (1H, *d*, *J* = 15.76 Hz,), 7.65 (2H, *d*, *J* = 8.36 Hz,), 7.76 (1H, *d*, *J* = 15.7 Hz,), 7.83 (2H, *d*, *J* = 8.36 Hz,), 10.59 (1H, *bs*, NH). 13C NMR (125 MHz, $CDCl_3$): δ 177.49, 139.28, 134.08, 132.91, 131.74, 130.35, 126.60, 123.75, 123.29, 117.62, 110.22.

1.1.23. *(E)-3-(3,4-Dimethoxyphenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one (JS23):* Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44 %. Found: C, 70.12; H, 5.92; N, 5.51 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (6H, *s*), 6.27 (1H, *d*, *J* = 2.45 Hz,), 7.01 (1H, *d*, *J* = 8.35 Hz,), 7.15 (1H, *s*) 7.35 (1H, *dd*, J = 1.83 and 8.35 Hz,), 7.38 (1H, *m*), 7.48 (1H, *d*, *J* = 1.74 Hz,), 7.56 (1H, *d*, *J* = 15.84 Hz,), 7.64 (1H, *d*, *J* = 15.84 Hz,), 10.55 (1H, *s*, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.83, 150.68, 148.8, 140.98, 133.07, 127.60, 125.94, 123.07, 120.60, 116.96, 111.44, 110.50, 109.88, 55.59, 55.45.

1.1.24. *(E)-3-(4-Methoxyphenyl)-1-(furan-2-yl)prop-2-en-1-one (JS24):* Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30 %. Found: C, 73.81; H, 5.34 %. ^{1}H NMR (500 MHz, CDCl3): δ 3.83 (3H, *s*), 6.58 (1H, *dd*, *J* = 1.68, 2.01 Hz), 6.92 (2H, *m*), 7.30 (1H, *d*, *J* = 4.4 Hz,), 7.32 (1H, *d*, *J* = 16.0 Hz,), 7.60 (2H, *m*), 7.63 (1H, *m*), 7.84 (1H, *d*, *J* = 16.0 Hz,). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.16, 161.76, 153.86, 146.32, 143.82, 130.34, 127.48, 118.85, 117.35, 114.43, 112.4, 55.41.

1.1.25. *(E)-3-(4-Bromophenyl)-1-(furan-2-yl)prop-2-en-1-one (JS25):* Anal. Calcd for $C_{13}H_9BrO_2$: C, 56.34, 3.27, H, 5.46 %. Found: C, 56.49, H, 3.29 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (1H, *m*), 7.35 (1H, *dd*, J = 1.6 & 3.2,), 7.44 (1H, *d*, *J* = 16.0 Hz,), 7.5 (2H, *dd*, *J* = 8.02 Hz and 1.63 Hz,), 7.66 (1H, *m*), 7.72 (2H, *dd*, *J* = 8.02 Hz and 1.63 Hz), 7.84 (1H, *d*, *J* = 16.0 Hz,). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.73, 153.62, 146.63, 142.53, 133.66, 132.21, 129.87, 124.89, 121.71, 117.68, 112.66.

1.1.26. *(E)-3-(3,4-Dimethoxyphenyl)-1-(furan-2-yl)prop-2-en-1-one (JS26):* Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46 %. Found: C, 69.88; H, 6.51 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (3H, *s*), 3.92 (3H, *s*), 6.71 (1H, *dd*, *J* = 1.65 and 3.51 Hz), 7.02 (1H, *d*, *J* = 8.24 Hz), 7.46 (4H, *m*), 7.81 (1H, *d*, *J* = 14.60 Hz), 7.85 (1H, *bs*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.43, 154.196, 151.86, 149.57, 148.67, 144.49, 128.07, 123.76, 119.34, 117.55, 112.88, 114.40, 110.42, 56.36.

1.1.27. *(E)-1-(4-methoxyphenyl)-3-(pyridin-4-yl)prop-2-en-1-one (JS27):* Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85 %. Found: C, 75.36; H, 5.87; N, 5.39 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (3H, *s*), 6.96 (2H, *d*, *J* = 7.2 Hz), 7.51 (2H, *d*, *J* = 7.4 Hz), 7.66-7.70 (3H, *m*), 7.88 (1H, *d*, *J* = 15.6 Hz), 8.71 (2H, *d*, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.06, 166.05, 149.72, 149.69, 144.08, 143.99, 130.09, 129.99, 129.68, 128.99, 121.07, 120.69, 114.08, 113.99, 54.99.

1.1.28. *(E)-1-(4-bromophenyl)-3-(pyridin-4-yl)prop-2-en-1-one (JS28):* Anal. Calcd for $C_{14}H_{10}BrNO$: C, 58.36; H, 3.50; Br, 27.73; N, 4.86 %. Found: C, 58.63; H, 3.70; Br, 27.79; N, 4.75 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.70 (7H, *m*), 7.93 (1H, *d*, *J* = 15.3 Hz), 8.77 (2H, *d*, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.99, 148.90, 147.99, 144.88, 143.92, 136.09. 133.11, 133.02, 131.93, 131.10, 128.09, 128.99, 120.71, 119.94.

1.1.29. *(E)-1-(4-hydroxyphenyl)-3-(pyridin-4-yl)prop-2-en-1-one (JS29):* Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22 %. Found: C, 74.76; H, 4.79; N, 6.33 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.25 (1H, *s*), 6.97 (2H, *d*, *J* = 7.7 Hz), 7.52-7.64 (5H, *m*), 7.91 (1H, *d*, *J* = 15.5 Hz), 8.88 (2H, *d*, *J* = 7.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.64, 164.31, 148.72, 148.69, 144.89, 143.99, 131.19, 130.05, 131.03, 128.11, 120.67, 120.69, 116.41, 115.99.

1.1.30. *(E)-1-(3,4-dimethoxyphenyl)-3-(pyridin-4-yl)prop-2-en-1-one (JS30):* Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20 %. Found: C, 71.72; H, 5.43; N, 5.51 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (6H, *s*), 6.85 (1H, *d*, *J* = 7.3 Hz), 7.21 (2H, *m*), 7.49-7.56 (3H, m), 7.97 (1H, *d*, *J* = 16.4 Hz), 8.69 (2H, *d*, *J* = 8.2 Hz). ^{13}C NMR (125

MHz, $CDCl_3$): δ 188.64, 154.99, 150.03, 148.99, 148.90, 143.96, 143.70, 131.19, 127.99, 123.02, 119.92, 115.08, 114.80, 56.2, 55.99.

1.1.31. *(E)-1-(4-methoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (JS31):* Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59 %. Found: C, 83.49; H, 5.36 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (1H, *d*, *J* = 15.3 Hz), 8.68 (1H, *d*, *J* = 8.4 Hz), 8.09 (2H, *d*, *J* = 9 Hz), 7.87-7.92 (3H, *m*), 7.48-7.65 (4H, m), 6.99 (2H, *d*, *J* = 8.7 Hz), 3.89 (3H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.03, 165.98, 145.12, 134.99, 131.11, 130.09, 129.99, 129.50, 128.08, 127.99, 126.11, 125.99, 125.08, 124.01, 123.01, 114.08, 113.99, 103.05, 53.99, 26.06.

1.1.32. *(E)-1-(4-bromophenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (JS32):* Anal. Calcd for $C_{19}H_{13}BrO$: C, 67.67; H, 3.89; Br, 23.70 %. Found: C, 67.73; H, 3.97; Br, 23.56 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.36 (4H, *m*), 7.55-7.67 (6H, *m*), 7.70 (2H, *d*, *J* = 8.9 Hz), 7.99 (1H, *d*, *J* = 15 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.44, 144.92, 136.09, 134.95, 132.19, 132.09, 131.98, 131.96, 131.92, 129.92, 128.90, 127.99, 127.03, 126.34, 126.01, 125.98, 125.69, 124.02, 123.02, 103.05.

1.1.33. *(E)-1-(3,4-dimethoxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (JS33):* Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70 %. Found: C, 79.28; H, 5.63 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (1H, *d*, *J* = 15 Hz), 8.30 (1H, *d*, *J* = 10 Hz), 7.91-7.96 (3H, *m*), 7.76 (1H, *dd*, *J* = 5 Hz and 10 Hz), 7.33-7.70 (5H, *m*), 6.93 (1H, *d*, *J* = 10 Hz), 4.02 (3H, *s*), 4.00 (3H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.09, 56.13, 110.05, 110.87, 123.17, 123.60, 124.48, 125.07, 125.45, 126.30, 126.93, 128.75, 130.61, 131.29, 131.77, 132.66, 133.74, 140.99, 149.30, 153.36, 188.43.

1.1.34. *(E)-1-(4-methoxyphenyl)-3-(naphthalen-3-yl)prop-2-en-1-one (JS34):* Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59 %. Found: C, 83.46; H, 5.43 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (2H, *d*, *J* = 10 Hz), 8.04 (1H, *s*), 8.00 (1H, *d*, *J* = 15 Hz), 7.81-7.91 (4H, *m*), 7.69 (1H, *d*, *J* = 15 Hz), 7.52-7.56 (2H, *m*), 7.02 (2H, *d*, *J* = 10 Hz), (3.91 (3H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.51, 113.88, 122.01, 123.73, 126.73, 127.26, 127.80, 128.62, 128.68, 130.43, 130.85, 131.18, 132.99, 133.40, 134.30, 144.04, 163.45, 188.65.

1.1.35. *(E)-1-(4-hydroxyphenyl)-3-(naphthalen-3-yl)prop-2-en-1-one (JS35):* Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14 %. Found: C, 83.28; H, 5.01 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.32 (1H, s), 6.99 (2H, *d*, *J* = 8.8 Hz), 7.32-7.36 (3H, *m*), 7.55-7.70 (7H, *m*), 7.99 (1H, *d*, *J* = 16.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.01, 165.10, 145.50, 132.91, 131.94, 131.02, 130.91, 130.92, 129.76, 18.02, 127.89, 127.07, 125.67, 125.50, 124.45, 123.05, 120.74, 114.89, 114.67.

1.1.36. *(E)-1-(3,4-dimethoxyphenyl)-3-(naphthalen-3-yl)prop-2-en-1-one (JS36):* Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70 %. Found: C, 79.11; H, 5.63 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (6H, s), 6.88 (1H, *d*, *J* = 8 Hz), 7.20-7.35 (5H, m), 7.52 (1H, *d*, *J* = 15.8 Hz), 7.65-7.72 (4H, m), 7.95 (1H, *d*, *J* = 15.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.73, 154.83, 150.03, 145.02, 133.06, 133.19, 132.99, 131.78, 128.12, 127.99, 127.07, 125.78, 125.50, 124.76, 123.05, 123.01, 120.95, 115.07, 114.91, 55.89, 54.78.

1.1.37. *(E)-3-(1H-indol-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (JS37):* Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05 %. Found: C, 77.83; H, 5.47; N, 4.89 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (3H, *s*), 6.96-7.00 (6H, *m*), 7.56-7.70 (3H, *m*), 7.98 (1H, *d*, *J* = 15.4 Hz), 9.30 (1H, *s*), 10.1 (1H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.92, 165.60, 143.20, 135.05, 130.09, 130.03, 129.34, 129.01, 127.45, 125.87, 122.45, 119.45, 119.03, 114.08, 113.78, 111.09, 110.01, 53.78.

1.1.38. *(E)-1-(4-bromophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (JS38):* Anal. Calcd for $C_{17}H_{12}BrNO$: C, 62.60; H, 3.71; Br, 24.50; N, 4.29 %. Found: C, 62.71; H, 3.83; Br, 24.29; N, 4.11 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98-7.02 (4H, *m*), 7.57-7.69 (5H, *m*), 7.89 (1H, *d*, *J* = 15.2 Hz), 9.33 (1H, *s*), 9.99 (1H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.50, 143.29, 136.09, 135.55, 132.28, 132.21, 131.89, 130.45, 130.09, 127.99, 127.23, 126.32, 122.45, 119.32, 118.34, 110.34, 109.21.

1.1.39. *(E)-1-(4-hydroxyphenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (JS39):* Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32 %. Found: C, 77.66; H, 4.73; N, 5.46 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (1H, *s*), 6.93-7.11 (6H, *m*), 7.55-7.65 (3H, *m*), 8.00 (1H, *d*, *J* = 15.1 Hz), 9.13 (1H, *s*), 10.11 (1H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.75, 163.69, 145.29, 134.97, 131.89, 130.67, 130.43, 129.34, 126.78, 125.99, 123.01, 120.56, 119.43, 115.23, 115.01, 112.98, 110.23.

1.1.40. *(E)-3-(1H-indol-3-yl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (JS40):* Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56 %. Found: C, 74.36; H, 5.28; N, 4.39 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.08 (1H, *s*), 9.08 (1H, *s*), 8.33-8.35 (1H, *m*), 8.13 (1H, *d*, *J* = 15 Hz), 8.04-8.06 (1H, *m*), 7.86 (1H, *d*, *J* = 5 Hz), 7.55 (1H, *s*), 7.31-7.34 (3H, *m*), 6.91 (1H, *d*, *J* = 10 Hz), 3.98 (3H, *s*), 3.89 (3H, *s*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.98, 56.07, 111.56, 111.97, 117.49, 120.65, 121.62, 121.94, 122.59, 122.95, 123.30, 123.42, 130.07, 132.07, 135.44, 138.09, 149.00, 152.81, 185.12.

2.1. Preparation of sperm suspension

Human semen samples were obtained from young, healthy, and fertile volunteers in a sterile vial by masturbation with average sperm concentration ranging from 75 to 90 X 10^6/mL, normal morphology of more than 60% and grade A motility of more than 40%, with more than 70% sperm viability, were used for this study. Semen samples were collected after 72–96 h of sexual abstinence. Routine semen analysis was done after liquefaction of semen at 37ºC [21].

2.2. Sperm motility

Minimum effective (spermicidal) concentration (MEC) was determined by the standard procedure. Briefly, the test compounds were dissolved in a minimum volume of arachis oil and diluted with arachis oil to make a 1.0% (10 mg/ml) solution. The solutions were further diluted serially with arachis oil. A spermicidal test was performed with each dilution starting from 1.0% until the minimum effective concentration (MEC) was arrived. For this purpose 0.05 ml of liquefied human semen was added to 0.25 ml of test solution and vortexed for 10 s. A drop of the mixture was immediately placed on a microscope slide, covered with a cover glass and immediately examined at 40 X under phase contrast microscope (Olympus) in five fields of vision. The results were scored positive if 100% spermatozoa became immotile in 20 s. The MEC was determined in three individual semen samples from different donors. The minimum concentration of compound capable of killing 100% sperm in 20 s in ‘‘all’’ the semen samples was denoted as MEC and is recorded in Table 2, whereas even if only one or two spermatozoa showed sluggish motility, the test concentration of the compound was scored negative. The control slides were prepared by adding physiological saline instead of test solutions.

2.3. Sperm revival test

After the completion of the experiment, the spermatozoa were washed twice in arachis oil and incubated once again in test compound-free media at 37ºC for 30 min to observe a reversal of sperm motility. The above study was repeated three times using semen from the same individuals as well as from different individuals [22].

2.4. Sperm viability

Supravital staining with fluorescent dye (Eosin nigrosin) [23] and the hypo-osmotic swelling test (HOST) were used to assess the effect of compounds on sperm cell viability. A 0.2 ml aliquot of liquefied semen was treated with 1.0 ml of spermicide solution (1.0%) and incubated for 1 min at 37ºC. The spermatozoa were pelleted by centrifugation and 0.2 ml of 1% eosin Y was added to the pellet and mixed gently. After 30 s, 0.4 ml of 10% nigrosin were added and mixed well. The mixture was incubated for 15 min at 37ºC. A wet mount for each compound was observed under the 40 X phase contrast microscope (Olympus) and the number of fluorescent (red) sperm heads was recorded. The same was repeated for other fields of view.

The HOST experiment was used to determine the effect on the physiological integrity of the sperm membrane. Human spermatozoa treated with spermicide solution (as in the supravital staining experiment) were pelleted, treated with hypo-osmotic solution (sodium citrate 25 mM/fructose 75 mM; 150 mosmol), and mixed gently. The suspension was incubated for 30 min at 37 ºC. A wet mount was prepared for each compound solution and observed under a phase contrast microscope, and spermatozoa with and without tail curling were counted and recorded in different fields of view. The percentage of HOST-negative (HOST-ve) and Eosin nigrosin-stained sperm (mean of three values) has been presented in Figure 2.

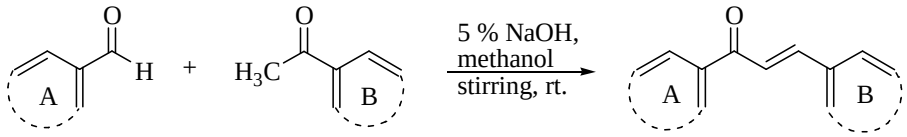
2.5. Acrosome status and function test

The acrosome status and function test was done according to the method of Gopalkrishnan [24]. Gelatin coat was prepared on a clean glass slide. After 24 h, the slides were fixed in 0.05% glutaraldehyde. On the day of experiment, semen samples were diluted with PBS–D-glucose. With 20 AL of diluted semen, a smear was prepared on the gelatin slide. The slides were incubated at 37ºC for 2 h. Acrosomal enzymes dissolve the gelatin and create holes. Spermatozoa with holes are counted against those without holes, and the percentage was noted.

RESULTS AND DISCUSSION

2.1. Synthesis

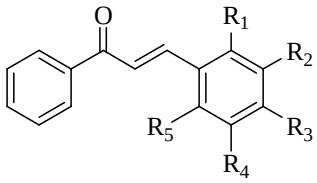
In the present investigation, 40 chalcone-like molecules viz (E)-3-(substituted aryl/heteroaryl)-1-substitutedphenylprop-2-en-1-ones have been synthesized via Claisen Schmidt condensation of aryl ketones and aryl aldehydes under basic conditions (Scheme 1) The method is attractive as it selectively yields E isomer from ^{1}H NMR. All diaryl propenones were found to be geometrically pure and with *trans* configuration ($J \geq 15$ Hz). The synthesized chemical entities (JS1–JS40) with diversification in chemical structures are shown in Table 1. The synthesized compounds were characterized by elemental analysis, ^{1}H and ^{13}C NMR.



I and II

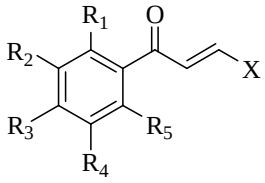
Scheme 1: Synthesis of (E)-3-(aryl/heteroaryl)-1-phenylprop-2-en-1-ones by Claisen–Schmidt condensation of substituted aryl ketone with substituted aromatic aldehydes

Table 1. The synthesized chemical entities (JS1–JS40) with diversification in chemical structures



I

Entry	Substitution					Yield (%)	m.p. (°C)
	R_1	R_2	R_3	R_4	R_5		
JS1	H	H	H	H	H	89	80-81 °C
JS2	H	H	F	H	H	92	116-117 °C
JS3	H	H	Cl	H	H	95	132-133 °C
JS4	H	H	Br	H	H	97	150-151 °C
JS5	H	H	NO_2	H	H	90	138-139 °C
JS6	H	H	OCH_3	H	H	85	95-96 °C
JS7	H	H	H	Cl	H	93	125-126 °C
JS8	H	H	H	H	OCH_3	83	100-101 °C
JS9	H	H	OCH_3	OCH_3	H	81	119-120 °C



II

Entry	Substitution						Yield (%)	m.p. (°C)
	R_1	R_2	R_3	R_4	R_5	X		
JS10	H	H	H	H	H	Thiophen-2-yl	81	93-94 °C
JS11	H	H	H	H	H	Pyrrol-2-yl	69	195-196 °C
JS12	H	H	H	H	H	Furan-2-yl	79	87-88 °C
JS13	H	H	H	H	H	Pyridin-4-yl	72	181-182 °C
JS14	H	H	H	H	H	Naphth-1-yl	87	111-112 °C
JS15	H	H	H	H	H	Naphth-2-yl	88	110-111 °C
JS16	H	H	H	H	H	Indol-3-yl	75	169-170 °C
JS17	H	H	OCH_3	H	H	Thiophen-2-yl	77	105-106 °C
JS18	H	H	Br	H	H	Thiophen-2-yl	71	155-156 °C
JS19	H	H	OH	H	H	Thiophen-2-yl	74	110-111 °C
JS20	H	H	OCH_3	OCH_3	H	Thiophen-2-yl	65	121-122 °C

JS21	H	H	OCH_3	H	H	Pyrrol-2-yl	63	137-138 °C
JS22	H	H	Br	H	H	Pyrrol-2-yl	67	178-179 °C
JS23	H	H	OCH_3	OCH_3	H	Pyrrol-2-yl	61	166-167 °C
JS24	H	H	OCH_3	H	H	Furan-2-yl	73	82-83 °C
JS25	H	H	Br	H	H	Furan-2-yl	78	131-132 °C
JS26	H	H	OCH_3	OCH_3	H	Furan-2-yl	70	109-110 °C
JS27	H	H	OCH_3	H	H	Pyridin-4-yl	69	167-168 °C
JS28	H	H	Br	H	H	Pyridin-4-yl	62	192-193 °C
JS29	H	H	OH	H	H	Pyridin-4-yl	66	157-158 °C
JS30	H	H	OCH_3	OCH_3	H	Pyridin-4-yl	60	173-174 °C
JS31	H	H	OCH_3	H	H	Naphth-1-yl	81	120-121 °C
JS32	H	H	Br	H	H	Naphth-1-yl	83	144-145 °C
JS33	H	H	OCH_3	OCH_3	H	Naphth-1-yl	88	156-157 °C
JS34	H	H	OCH_3	H	H	Naphth-2-yl	89	123-124 °C
JS35	H	H	OH	H	H	Naphth-2-yl	82	130-131 °C
JS36	H	H	OCH_3	OCH_3	H	Naphth-2-yl	84	149-150 °C
JS37	H	H	OCH_3	H	H	Indol-3-yl	71	188-189 °C
JS38	H	H	Br	H	H	Indol-3-yl	67	221-222 °C
JS39	H	H	OH	H	H	Indol-3-yl	78	199-200 °C
JS40	H	H	OCH_3	OCH_3	H	Indol-3-yl	61	200-201 °C

The results of effect on sperm motility of compounds (JS1-JS40) provide an interesting structure–activity relationship and suggest that the nature of Ring A and Ring B play an important role in the regulating sperm motility. Keeping phenyl ring as Ring A: 1) Methoxy substituent on phenyl ring as Ring B improves the activity whereas substitution with halo group drastically reduces the activity. 2) Nitro group substitution on phenyl ring as Ring B shows moderate activity. 3) Increase in the number of methoxy substituents on phenyl ring as Ring B improves the activity profile whereas change in the position of methoxy substituent does not show any effect on the spermicidal activity. 4) Replacement of phenyl with monocyclic heteroaryl ring as Ring B (Pyrrol, Furan, Thiophene, Pyridine) enhances the activity comparable to mono methoxy substituted phenyl ring whereas bicyclic aryl ring as Ring B (1-Naphthyl or 2-Naphthyl) act as a surrogate for dimethoxy substituted phenyl ring. 5) Placement of bicyclic heteroaryl ring as Ring B (Indole) significantly enhances the activity profile and proves to be the the most potent compound among the series. Any substitution on Ring A, irrespective of the substituent position completely diminishes the activity.

Table 2. Spermicidal MEC % of synthesized compounds

Entry	Spermicidal MEC %	Entry	Spermicidal MEC %
JS1	1	JS22	NA
JS2	NA	JS23	NA
JS3	NA	JS24	NA
JS4	NA	JS25	NA
JS5	1	JS26	NA
JS6	0.5	JS27	NA
JS7	NA	JS28	NA
JS8	0.5	JS29	NA
JS9	0.1	JS30	NA
JS10	0.5	JS31	NA
JS11	0.5	JS32	NA
JS12	0.5	JS33	NA
JS13	0.5	JS34	NA
JS14	0.1	JS35	NA
JS15	0.1	JS36	NA
JS16	0.05	JS37	NA
JS17	NA	JS38	NA
JS18	NA	JS39	NA
JS19	NA	JS40	NA
JS20	NA	Fluoxetine	0.05
JS21	NA	N-9	0.05

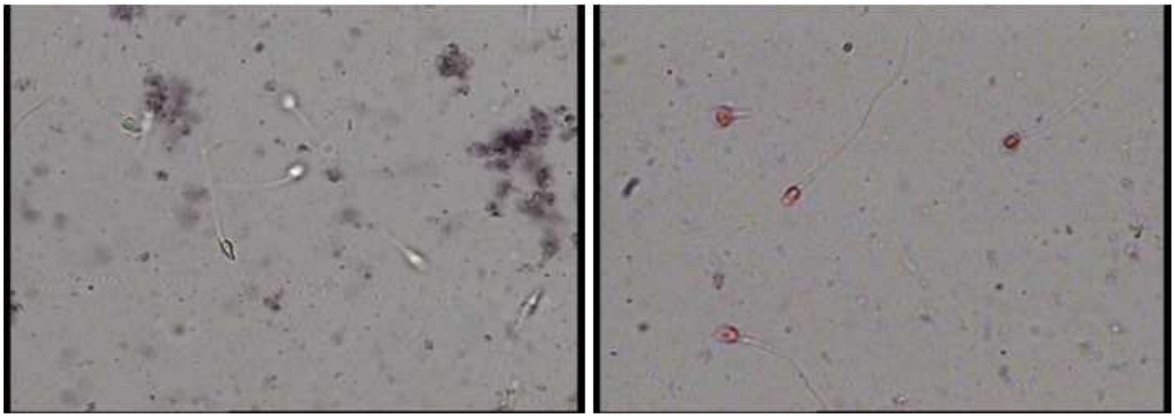
**NA = Not active*

2.2. Biological evaluation

2.2.1 Sperm motility and viability

The compounds listed in Table 1 were prepared and tested for their spermicidal activity. Twelve compounds (JS1, JS5, JS6, JS8-JS16) showed 100% spermicidal activity at a concentrations ranging from 0.05-1% (Table 2). Out of

these, four compounds (JS9, JS14-JS16) exhibited potent spermicidal activity with total immobilization of 100% spermatozoa within 20 s at the concentration less than or equal to 0.1%. Compounds (JS2, JS3, JS4, JS7, JS17-JS40) have no effect on sperm motility even at 1%. Compound JS16 was most active in this series as the sperm completely lost motility even at 0.05% concentration. Fluoxetine and N-9 showed spermicidal MEC of 0.05%. Sperm viability was almost in accordance to the sperm immobilization (Figure 2).



A **B**

Figure 2: Sperm viability assessment by Eosin-nigrosin staining. (A) Control sperm (B) compound JS16 treated sperm appeared red due to uptake of fluorescent dye (Eosin-nigrosin).

2.2.2. Sperm revival test

None of the spermatozoa, once immobilized by the test compound, regained their motility after removing the test compound and resuspending it in physiological saline followed by incubation at 37°C for 30 min.

2.2.3 Acrosome status and function

In the acrosome test, test compound (JS16) at the concentration of 1.0% showed 10% fewer number of holes in comparison to the control, but at a concentration of 0.5%, there was no significant change in hole formation seen immediately after exposure to JS16. But in both cases, the holes were reduced in size or had become irregular when compared to the control. At lower concentrations, there was no significant change in number as well as size of the hole compared to the control.

CONCLUSION

Preparation of a series of 40 chalcone-like derivatives and their spermicidal activities are described. Twelve compounds (JS1, JS5, JS6, JS8-JS16) showed 100% spermicidal activity at a concentrations ranging from 0.05-1% (Table 2). Out of these, four compounds (JS9, JS14-JS16) exhibited potent spermicidal activity with total immobilization of 100% spermatozoa within 20 s at the concentration less than or equal to 0.1%. Compounds (JS2, JS3, JS4, JS7, JS17-JS40) have no effect on sperm motility even at 1%. Compound JS16 was most active in this series as the sperm completely lost motility even at 0.05% concentration. Moreover, the motility could not be revived in the test compound-treated sperm when the compound was washed and replaced with fresh media. This reveals that the synthesized compounds caused irreversible damage to the sperm. The fertilizing ability of sperm is not only dependent on motility but also on other functional characteristics [25]. Therefore, besides motility, other parameters such as viability and hypo-osmotic swelling are now being increasingly assessed. Most of the spermicidal agents induce spermicidal effects by disrupting the plasma membrane as they act on sperm surface. In the present study, damage to the sperm membrane integrity is evidenced by the significant reduction in sperm viability. The sperm membrane allows transport of ions and molecules selectively, and this is essential for normal sperm motility. Therefore, sperm viability was almost in accordance to the sperm immobilization. Several spermicides cause drastic inhibition in sperm membrane-specific enzymes like acrosin and hyaluronidase, the most important enzymes in the process of fertilization. Marked decrease in the acrosome status indicates that the compound JS16 also caused damage to the outer acrosomal membrane. In conclusion, it has been demonstrated that the synthesized compounds possesses an immobilizing factor that probably reduces motility by causing sperm nonviability by disrupting the membrane architecture of the sperm cell. The result of this study finds compound JS16 as the lead molecule for the development of improved spermicidal agents.

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