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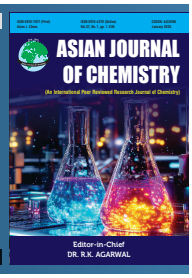

A Benign Lewis Acid Catalyzed Approach for Mannich Reaction: Straight Forward Synthesis of β-Amino Ketones using Simple Iron Salts as Catalyst

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In this approach, $FeCl_3$ was used as a moderate Lewis acid and an efficient catalyst to synthesize β-amino ketones *via* three-component Mannich reaction between series of substituted aromatic aldehyde, aryl amine and aryl ketones under mild conditions, where the Lewis acidic $FeCl_3$ facilitates both C-C and C-N bond formation simultaneously without any complicated catalyst preparations. An inexpensive, readily accessible $FeCl_3$ as an Lewis acid catalyst for synthesizing β-amino ketones through a straightforward tandem reaction in a one-pot protocol is unveiled with benefits like a short reaction time, rapid workup and good to outstanding yields under more eco-friendly conditions. This mild Lewis catalyst provides a sustainable and alternative method for obtaining synthetically necessary β-amino ketones under greener conditions. The present methodology opens the new doors for synthesizing substituted β-amino ketones and their chemical structures were verified by ^1H and ^{13}C NMR spectroscopic data. 1,3-Diphenyl-3-(phenylamino)propan-1-one (**4a**) was evaluated for antibacterial, antifungal, antioxidant and anticancer activities.

Keywords: Lewis acid, β-Amino ketones, Greener approach, Mannich reaction.

INTRODUCTION

A conventional technique for synthesizing amino ketones and aldehydes or Mannich bases is the Mannich reaction. It is a crucial stage in the production of many natural products, pharmaceutical compounds and multifunctional (active pharmaceutical) synthetic intermediates [1]. The Mannich reaction provides a straightforward and effective method for the synchronous formation of C-C and C-N bonds [2], various synthetic and catalytic techniques, as well as a variety of transition metal catalysts, offering a potential mechanism for creating such linkages. The two-component method of the classical Mannich reactions produced β-amino ketones [3] or three-component systems, which serve as adaptable synthetic building blocks for the formation of amino acids and nitrogen-containing compounds that are essential to life, such as lactams, peptides and amino alcohols [4]. As a result, the development of new synthetic techniques which produce β-amino carbonyl compounds or their derivatives has drawn lot of attention. By reducing the quantity of synthetic stages, energy usage and waste generation, Multicomponent reactions (MCRs) help to meet the demand for an environmentally sustainable process. As a result, the increasing need for the new MCRs is understandable [5,6].

Nevertheless, the conventional Mannich reaction presents numerous problems and its applications are inadequate [7]. To address the limitations of traditional methods, numerous contemporary versions of the Mannich reactions have been developed, employing electrophiles such as imines and stable nucleophiles including enolates, enol ethers and enamines [8]. Various synthetic and catalytic techniques, along with an array of transition metal catalysts, have proposed potential mechanisms for the formation of these linkages. It has been investigated constantly to create a more straightforward Mannich reaction methodology [9]. Furthermore, several distinct kinds of heterogeneous catalysts have undergone chemical modification are also employed as catalysts. The effective and protective Mannich reaction, for instance, variety of organocatalysts, including N-quaternized pyridoxal catalyst [10], silver tartaric acid-derived phosphate [11], ionic liquid-immobilized prolines [12], several squaramides based bi-functional organocatalyst [13], spiro phosphoric acids [14], metal salts like hafnium triflate [15], diaryliodonium salts, boric acid, $LiFe_5O_8$, silica-supported

aluminum chloride, magnetic solid sulfonic acids modified with hydrophobic regulators as ionic polymers, NH_2SO_3H and aryl boronic acid are reported in the ltierature.

The reactive and costly noble metals are gradually being replaced by less costly and readily available earth-abundant metals in the modern metal-catalyzed mediated organic synthesis [16]. Because of easy accessibility, handling and reactivity, iron salts are more appealing among them [17]. In the recent decades, little research has been done on the function of $FeCl_3$. Its use in a variety of transformations has only lately been gradually recognized and documented, $FeCl_3$ exhibits a great deal of catalytic potential. In this study, we have described a novel and eco-friendly method for synthesizing β-amino ketone derivatives, as well as the antibacterial, antifungal, antioxidant and anticancer activities of 1,3-diphenyl-3-(phenylamino)-propan-1-one (**4a**).

EXPERIMENTAL

All the reagents and solvents used were of spectral grade. The melting points of the compounds were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a BRUKER model using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as internal reference for all NMR spectra.

General procedure for $FeCl_3$ catalyzed synthesis of β-amino ketones: A mixture of benzaldehyde (1 mmol), aniline (1 mmol) and acetophenone (1 mmol) was thoroughly mixed with $FeCl_3$ (10 mol %) under solvent-free conditions in a clean, dry round-bottom flask. The resulting mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as eluent. Upon completion, the reaction mixture was allowed to cool to room temperature and then treated with 100 mL of cold distilled water. The compound was isolated by dissolving it in ethyl acetate and the catalyst was removed using filteration with aqueous washing. The ethyl acetate layer was then dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the crude product, which was recrystallized from ethanol (**Scheme-I**). All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectroscopic techniques.

1,3-Diphenyl-3-(phenylamino)propan-1-one (4a): Yield: 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.69-7.61 (m, 2H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.91-6.35 (m, 3H), 5.22 (t, *J* = 6.2 Hz, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (d), 129.15(s), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

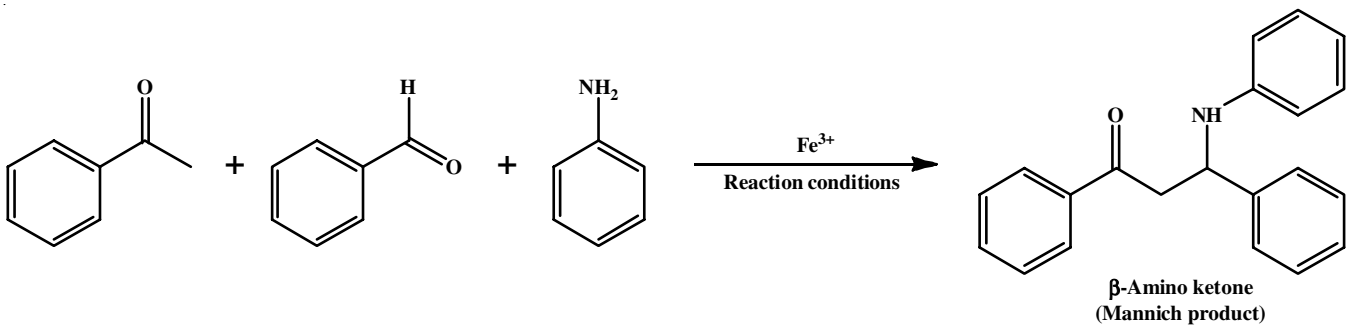
1-Phenyl-3-(phenylamino)-3-(*p*-tolyl)propan-1-one (4b): Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.98-7.72 (m, 1H), 7.69-7.61 (m, 2H), 7.56 (dd, *J* = 10.8, 4.5 Hz, 2H), 7.48 (dd, *J* = 15.8, 8.0 Hz, 2H), 7.21-7.06 (m, 2H), 7.04 (s, 1H), 6.87 (d, *J* = 12.8 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 2H), 5.11 (t, *J* = 6.2 Hz, 1H), 3.51 (t, *J* = 5.9 Hz, 2H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s), 24.15 (s).

1-Phenyl-3-(phenylamino)-3-(*m*-tolyl)propan-1-one (4c): Yield: 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.27 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.49-7.39 (m, 3H), 7.36-7.22 (m, 3H), 7.11 (t, *J* = 7.9 Hz, 2H), 6.80-6.52 (m, 3H), 5.04 (t, *J* = 6.3 Hz, 1H), 3.53 (d, *J* = 6.3 Hz, 2H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.14 (s), 142.37 (s), 129.48 (d), 126.72 (s), 124.26 (s), 114.26 (s), 77.83 (s), 77.40 (s), 76.98 (s), 55.33-55.06 (m), 46.65 (s).

3-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4d): Yield: 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.91 (d, *J* = 7.7 Hz, 2H), 7.58 (s, 1H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 1H), 7.21 (s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-(3-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4e): Yield: 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 3H), 7.36-7.29 (m, 1H), 7.25 (dd, *J* = 17.2, 9.9 Hz, 2H), 7.09 (t, *J* = 7.9 Hz, 2H), 6.79-6.48 (m, 3H), 5.14-4.87 (m, 1H), 3.47 (ddd, *J* = 23.7, 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.64 (s), 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s).

3-(4-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4f): Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm:



Scheme-I

7.91 (d, *J* = 7.7 Hz, 2H), 7.62 (d, *J* = 13.5 Hz, 1H), 7.60-7.50 (m, 1H), 7.45 (d, *J* = 7.5 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27-7.19 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.89-6.39 (m, 3H), 5.10-4.87 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.98 (s), 137.14 (s), 133.82 (s), 129.72-128.47 (m), 128.01-127.63 (m), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-(3-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4g): Yield: 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 10.7 Hz, 1H), 7.60-7.52 (m, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27-7.20 (m, 1H), 7.11 (s, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H), 2.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-(2-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4h): Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.62 (d, *J* = 13.5 Hz, 1H), 7.60-7.50 (m, 2H), 7.45 (d, *J* = 7.5 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27-7.19 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.89-6.39 (m, 3H), 5.10-4.87 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.98 (s), 137.14 (s), 133.82 (s), 129.72-128.47 (m), 128.01-127.63 (m), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-(4-Fluorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4i): Yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 6.9 Hz, 1H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.41 (s, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.91-6.35 (m, 3H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-(4-Nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4j): Yield: 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.95 (t, *J* = 18.1 Hz, 2H), 7.64-7.49 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 3H), 7.28 (dt, *J* = 27.1, 7.1 Hz, 3H), 7.09 (t, *J* = 7.9 Hz, 2H), 6.83-6.39 (m, 3H), 5.14-4.87 (m, 1H), 3.47 (ddd, *J* = 23.7, 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.64 (s), 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s).

3-(2-Nitrophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4k): Yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 3H), 7.28 (dt, *J* = 27.1, 7.1 Hz, 3H), 7.09 (t, *J* = 7.9 Hz, 2H), 6.92-6.28 (m, 3H), 5.16-4.80 (m, 1H), 3.47 (ddd, *J* = 23.7, 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.64 (s), 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s).

4-(3-Oxo-3-phenyl-1-(phenylamino)propyl)benzonitrile (4l): : Yield: 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 10.5 Hz, 1H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27-7.19 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 2H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

1-Phenyl-3-(phenylamino)-3-(pyridin-4-yl)propan-1-one (4m): : Yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 12.4 Hz, 1H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 6.2 Hz, 1H), 7.21 (s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H), 2.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.38-128.47 (m), 127.77 (s), 126.79 (s), 122.66 (s), 120.91 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

1,3-Diphenyl-3-(*p*-tolylamino)propan-1-one (4n): Yield: 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.98-7.72 (m, 1H), 7.69-7.61 (m, 2H), 7.56 (dd, *J* = 10.8, 4.5 Hz, 2H), 7.48 (dd, *J* = 15.8, 8.0 Hz, 2H), 7.21-7.06 (m, 2H), 7.04 (s, 1H), 6.87 (d, *J* = 12.8 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 5.11 (t, *J* = 6.2 Hz, 1H), 3.51 (t, *J* = 5.9 Hz, 2H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s), 24.15 (s).

3-((4-Methoxyphenyl)amino)-1,3-diphenylpropan-1-one (4o): Yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.91 (s, 1H), 8.01 (s, 2H), 7.85 (s, 2H), 7.55 (d, *J* = 23.6 Hz, 6H), 6.98 (d, *J* = 16.3 Hz, 5H), 4.31 (s, 1H), 3.87 (s, 3H), 2.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.38 (s), 145.25-144.99 (m), 143.37 (s), 133.79 (s), 129.62-128.45 (m), 127.73 (s), 126.76 (s), 118.16 (s), 114.21 (s), 77.86 (s), 77.43 (s), 77.01 (s), 55.19 (s), 46.70 (s), 31.31 (s).

3-((4-Bromophenyl)amino)-1,3-diphenylpropan-1-one (4p): Yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.91-6.35 (m, 3H), 5.22-4.79 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.14 (s), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

3-((4-Nitrophenyl)amino)-1,3-diphenylpropan-1-one (4q): Yield: 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.39-7.18 (m, 3H), 7.09 (t, *J* = 7.9 Hz, 2H), 6.84-6.38 (m, 3H), 5.22-4.77 (m, 1H), 3.47 (ddd, *J* = 23.7, 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.64 (s), 133.80 (s), 129.49 (s), 129.14 (d), 128.59 (s), 127.76 (s), 126.78 (s), 118.28 (s), 114.31 (s), 77.83 (s), 77.41 (s), 76.99 (s), 55.30 (s), 46.64 (s).

1,3-Diphenyl-3-(pyridin-4-ylamino)propan-1-one (4r): Yield: 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.7 Hz, 2H), 7.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27-7.18 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 2H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.07-4.97 (m, 1H), 3.47 (qd, *J* = 16.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 147.26 (s), 143.28 (s), 137.11 (d), 133.82 (s), 129.72-128.47 (m), 127.77 (s), 126.79 (s), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s).

1-(4-Chlorophenyl)-3-phenyl-3-(phenylamino)propan-1-one (4s): : Yield: 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.94 (d, *J* = 8.2 Hz, 2H), 7.58 (dd, *J* = 10.6, 4.0 Hz, 1H), 7.52-7.43 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 2H), 5.14-4.96 (m, 1H), 4.58 (s, 1H), 3.49 (qd, *J* = 16.2, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.42 (s), 147.57-147.30 (m), 137.04 (s), 133.80 (s), 129.62-128.81 (m), 128.59 (s), 127.74 (s), 126.75 (s), 118.17 (s), 114.21 (s), 77.84 (s), 77.41 (s), 76.99 (s), 55.20 (s), 46.70 (s).

1-(4-Nitrophenyl)-3-phenyl-3-(phenylamino)propan-1-one (4t): : Yield: 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.91 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 4H), 7.27 (dt, *J* = 15.5, 7.2 Hz, 3H), 7.08 (t, *J* = 7.7 Hz, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 5.10-4.88 (m, 1H), 3.46 (dd, *J* = 13.1, 6.3 Hz, 2H), 1.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 198.65 (s), 164.88 (s), 153.92 (s), 153.37 (s), 147.26 (s), 143.28 (s), 137.01 (d), 133.82 (s), 129.50 (s), 129.15 (d), 128.60 (s), 127.77 (s), 126.79 (s), 120.87-120.61 (m), 120.24-119.98 (m), 118.28 (s), 114.30 (s), 77.85 (s), 77.43 (s), 77.01 (s), 55.29 (s), 46.66 (s)

Antimicrobial activity: The antibacterial and antifungal activitives of compound **4a** were exhibited against two Gram-positive bacterial strains *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 441) and two Gram-negative bacterial strains *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688) and for fungal culture used in the study were *Candida albicans* (MTCC 183), *Candida vulgaris* (MTCC 184), *Aspergillus niger* (MTCC 282), *Aspergillus flavus* (MTCC 277) were prepared as test organisms. All the bacterial strains were purchased from the Microbial Type Culture and Collection (MTCC) at Chandigarh, India and the fungal strains from National Chemical Laboratory (NCL), Pune, India.

Determination of antibacterial activity by disc diffusion method: The antibacterial activity was assessed using the disc diffusion method. The test organism was inoculated into sterile petri dishes with a 60 mm diameter after 10 mL of Mueller-Hilton agar medium was added. Mueller-Hilton agar plates were covered with sterile filter paper discs loaded with samples at concentrations of 60, 80 and 100 µg/mL. As a positive control, a filter paper disc containing 5 µg of amoxicillin was employed. The experiment was done twice and the plates were incubated for 24 h at 37 ºC. The zone of inhibition was measured in millimeters.

Determination of antifungal activity by disc diffusion method: To test the antifungal activity of compound **4a** against test microorganisms, the disc diffusion method was also used. A sterile filter paper disc (6 mm diameter, Whatman paper no. 3) was placed into 60 mm petri dishes inoculated with 0.3 mL of test organism and filled with Sabouraud's dextrose agar (SDA). Compound **4a** (10 µL) at different concentrations of 60, 80 and 100 µL were used to saturate the sterile disc. After 24 h of incubation at 37 ºC, the zones of growth inhibition surrounding the disc were assessed, with fluconazole serving as a positive control.

Antioxidant activity of the compound

DPPH assay method: Using steady DPPH free radical activity, antioxidant capacity of compound **4a** was assessed. Compound **4a** (1000 µL) at varying quantities (20-100 µL) were mixed with 500 µL of an ethanolic solution of DPPH (0.05 mM). At 4 ºC, the freshly made DPPH solution was stored in dark. The liquid was then forcefully agitated after 96% (2.7 mL) of ethanol was added. After letting the combination remain for 5 min at 540 nm, the absorbance was determined using spectrophotometry. Using ethanol, the absorbance was set to zero. The same quantity of DPPH and ethanol was used to prepare a blank sample. The radical activity of the material under test was determined as a percentage of inhibition.

$$\text{Inhibition of DPPH activity (\%)} = \frac{A - B}{A} \times 100$$

Anticancer activity: Breast cancer (MCF-7) cell lines were procured from the cell repository of the National Centre for Cell Sciences (NCCS), Pune, India. Dulbecco's modified eagle media (DMEM) was used for maintaining the cell line, which was supplemented with 10% fetal bovine serum (FBS). Penicillin (100 µg/mL) and streptomycin (100 µg/mL) were added to the medium to prevent the bacterial contamination. The medium with cell lines was maintained in a humidified environment with 5% CO_2 at 37 ºC. The cytotoxicity of breast cancer (MCF-7) cells was determined as reported by the method of Mosmann [18]. MTT (50 mg) dye was dissolved in 10 mL of PBS. After vortexing for 1 min, it was filtered through 0.45 micro filters. The bottle was wrapped with aluminium foil to prevent light, as MTT was light-sensitive. The preparation was stored at 4 ºC. The MCF-7 viable cells were harvested and counted using a hemocytometer, diluted in DMEM medium to a density of 1×10^4 cells/mL and seeded in 96-well plates for each well and incubated for 24 h to allow attachment. MCF-7 cells were treated with the different concentrations of compound **4a** (5 to 25 µg/mL) for 24 h at 37 ºC in a humidified 95% air and 5% CO_2 incubator for 24 h. After incubation, the drug-containing cells were washed with fresh culture medium and the MTT (5 mg/mL in PBS) solution was added to each well and incubated for another 4 h at 37 ºC. The purple precipitated

formazan formed was dissolved in 100 µL of DMSO and the cell viability was measured by taking the absorbance at 540 nm using a microplate reader. The results were expressed as the percentage of viable cells with respect to the control. All experiments were performed at least three times in triplicate. The viability percentage was calculated using the following formula. The IC_{50} values were determined from the compound **4a** dose responsive curve where inhibition of 50% cytotoxicity compared to control cells.

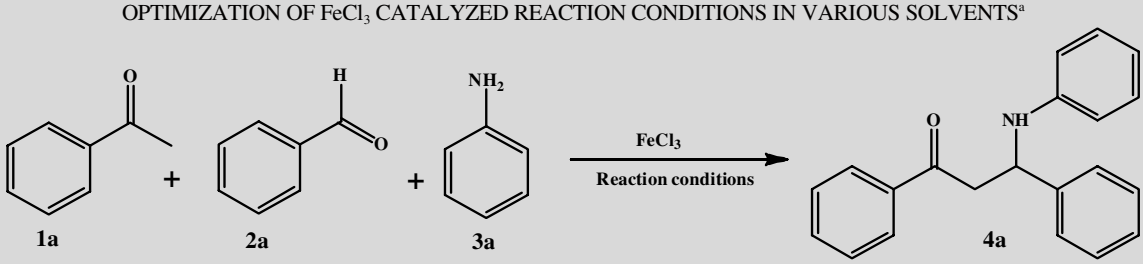
$$\text{Cell viability (\%)} = \frac{A_{sample} - A_{blank}}{A_{control} - A_{sample}} \times 100$$

RESULTS AND DISCUSSION

The catalyst utilized in this Mannich reaction, $FeCl_3$, was obtained commercially and did not require further purification. Because of its Lewis acidic nature in organic transformations, the potential of $FeCl_3$ for the production of synthetically relevant β-amino ketones was investigated. The goal of this work was to develop a straightforward catalytic process for the ligand-free synthesis of β-amino ketones using easily accessible transition metals as a catalyst. To investigate $FeCl_3$ as a Lewis acidic catalyst in the production of β-amino ketones through one-pot three-component condensation reaction parameters that influence the catalytic behaviours of the $FeCl_3$ were optimized using acetophenone (**1a**) (1 mmol), benzaldehyde (**2a**) (1 mmol) and aniline (**3a**) (1 mmol) as a model substrates. To identify a reliable reaction condition, the first different solvents were screened (Table-1). Due to the good dispersibility nature of the $FeCl_3$ in an alcoholic medium, initially, the reaction was tested in different alcohols such as methanol, ethanol and isopropyl alcohol using 10 mol % $FeCl_3$ as catalyst and 24 h as reaction time. Among the used alcohols, in ethanol medium $FeCl_3$ exhibited excellent reactivity with 96% of isolated yield (96%, entry 10 and 11, Table-1); further to explore the better reactivity of $FeCl_3$, other solvents such as toluene, chloroform and THF were also screened, however, moderate reactivity was only observed. Next, water and DMF were screened to study the role of high-polar solvents. Latter one, DMF gave a good yield, whereas in water, though $FeCl_3$ has a solubility and hydration nature, it resulted in a poor yield. This might be due to the substrate's lack of solubility and poor mass transfer of substrates to the catalyst. Though the moderate reactivity was observed in water, further to tune the reactivity an aqueous mixture of ethanol was tested. However, it also ended with a poor yield. On the other hand, though ethanol has given better yield, from a green chemistry point of view, a solvent-free neat condition has also been tried. Under the solvent-free neat condition $FeCl_3$ showed excellent reactivity. The observed result almost changed the course of the reaction. Under neat conditions, the obtained yield is around 98%. All the above results concluded that solvent-free neat condition is a suitable reaction condition for the $FeCl_3$-catalyzed synthesis of β-amino ketones.

This screening studies showed that the complete conversion was reached within 1 h and only 10 mol% $FeCl_3$ loading is adequate to get an excellent yield (98%, Table-1, entries 12). From the screening studies, it is concluded that the as-prepared $FeCl_3$ acts as a catalyst for the synthesis of β-amino ketones in a solvent-free neat condition using 10 mol % of catalyst at the ambient temperature in 1 h. With the mild optimized reaction condition, to explore the inherent potential of $FeCl_3$ as a catalyst in synthetic chemistry, the synthesis of β-amino ketones was successfully extended using a series of aromatic aldehydes

TABLE-1
OPTIMIZATION OF $FeCl_3$ CATALYZED REACTION CONDITIONS IN VARIOUS SOLVENTS[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	Methanol	24	72
2	Ethanol	24	96
3	*iso*propyl alcohol	24	68
4	Toluene	24	36
5	$CHCl_3$	24	70
6	THF	24	52
7	DMF	24	76
8	Water	24	10
9	EtOH:water[c]	24	13
10	Ethanol	–	82[d], 70[e], 67[f]
11	Ethanol	24	96
12	Neat	1	98[g]
13	Neat	1	96[i], 96[j],
14	Neat	1	–[l]

[a]Reaction conditions: Benzaldehyde (1 mmol), acetophenone (1 mmol) and aniline (1 mmol), at stirring 24 h, [b]isolated yield. [c]1:1 ratio, Reaction time: [d]12 h, [e]5 h, [f]3 h, $FeCl_3$ load: [g]10 mol %, [j]20 mol %, [i]30 mol %, [l]without catalyst.

with other substituted anilines and acetophenone, which afforded the respective products in good to excellent yield (90-96%) without any byproducts or impurities.

Control experiments were conducted using other similar types of materials (Table-2) such as $Fe(NO_3)_3·9H_2O$, $FeSO_4$ *etc.* after examining the scope of $FeCl_3$ catalyst in the Mannich reaction with minimum catalyst loading under ambient conditions to demonstrate the inherent catalytic activity of $FeCl_3$ and to understand the catalytic active sites that are responsible for this transformation. Under the ideal circumstances, all were completely unresponsive (Table-2), which shows that Lewis acid $FeCl_3$ electrons are acting as catalytic sites. Remarkably, the previous reports [19,20] and based on the experimental observations.

In (Table-3), the flexibility of the substrate was also observed. All of the aldehydes (**4a-l**) underwent the reaction efficiently under the optimal conditions and were given the relevant products. This catalyst exhibits good to excellent isolated yield for a broad range of *para* and *meta*-substituted aryl aldehydes with both electron-releasing substituents, such as methyl groups (**4b-c**, Table-3) and electron-withdrawing substituents, such as chloro, bromo, fluoro, nitro and nitrile groups (**4d-l**, Table-3). However, a mild yield drop was observed when identical substituents were present in the *ortho*-position (**4h**, **4k**). Similarly, nitrile-substituted aldehyde (**4l**) and heteroaryl aldehyde, 4-pyridine carboxaldehyde (**4m**), produced moderate yields in comparison to other electron-withdrawing groups. Next, while examining the role of substituents on aniline (**4n-r**), no discernible changes were found. Good to exceptional yield was found regardless of the electronic character of the aniline substituents. However, the yields of heteroamines, including pyridine-4-amine (**4r**), were only moderate. The reaction is observed to be suppressed when nitrogen is present on either the aniline or aldehyde ring system, leading to an average yield (**4m** and **4r**, Table-3). The catalytic acidic sites of $FeCl_3$ were hindered due to the catalytic poisoning of the pyridine moiety. Additionally, acetophenone (**4s-t**) motif's role for substitutions was also evaluated. In contrast to electron-releasing (**4t**) replacements, the results showed that acetophenone with electron-withdrawing substituents went smoothly and produced an excellent yield. The reaction was also carried out on a gram scale to show the present catalyst's capability for the preparative purpose. The isolated yield (**4j**, Table-3) is similar to the results obtained for a small-scale reaction.

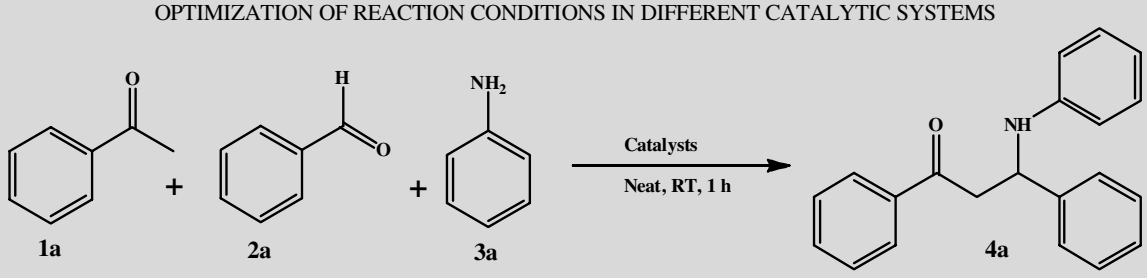
Further different catalysts are compared with the catalytic potential of $FeCl_3$ in the synthesis of β-amino ketones (**4a**) which is shown in Table-4. The benefits of $FeCl_3$ as a solid Lewis acid catalyst for the current Mannich process are amply supported by comparisons of the $FeCl_3$-catalyzed Mannich reaction with the current catalytic systems mentioned in Table-4. According to the comparison table, the $FeCl_3$ is a Lewis acid catalyst that is easy to obtain and requires no ligands and exhibits strong reactivity even at low catalyst loads.

Antimicrobial activity of compound 4a

***In vitro* antibacterial activity:** The results of the antibacterial activity of compound **4a** against different microorganisms by disc diffusions method are shown in Table-5. Compound **4a** showed inhibitory activity against *Staphylococcus aureus* (12 mm), *Pseudomonas aeruginosa* (8 mm), *Bacillus subtilis* (6 mm) and *Escherichia coli* (8 mm) at a concentration 100 µg/mL. At 80 µg/mL concentration, compound **4a** exhibited the antibacterial activity against all the tested bacteria, but it was more susceptible against *S. aureus* (9 mm). As the concentration of compound **4a** increased from 60-80 µg/mL, the inhibitory actions of the sample increased towards all the strains used in this study.

***In vitro* antifungal activity:** The antifungal susceptibility test of the different concentration of compound **4a** against the tested organisms is showed in Table-6. The highest activity was demonstrated against *C. albicans* (10 mm) at 100 µg/mL, followed by *C. vulgaris* (6 mm), *A. niger* (7 mm) and *A. flavus*

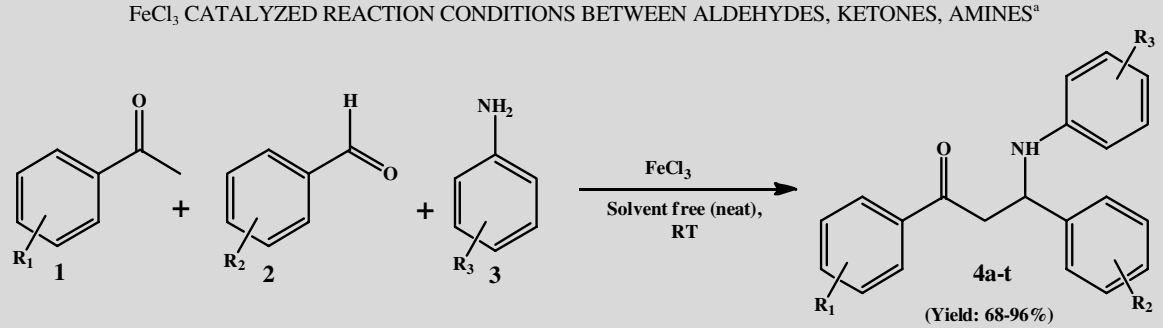
TABLE-2
OPTIMIZATION OF REACTION CONDITIONS IN DIFFERENT CATALYTIC SYSTEMS



Entry	Catalysts[b]	Yield[c]
1	$FeCl_2$	32
2	Nano-Fe_2O_3	5
3	$FeSO_4$	–
4	$Fe(NO_3)_3·9H_2O$	5
5	Fe(III)acac	12
6	$Fe_2(SO_4)_3$	62
7	$FeCl_3$	96
8	–	0

[a]Reaction conditions: Reactants benzaldehyde (1 mmol), acetophenone (1 mmol) and aniline (1 mmol), [b]Catalyst 10 mol %, [c]Isolated yield 1 h, Neat condition.

TABLE-3
$FeCl_3$ CATALYZED REACTION CONDITIONS BETWEEN ALDEHYDES, KETONES, AMINES[a]



Entry	R_1	R_2	R_3	Product[b]	Time (min)	Yield (%)
1	H	H	H	**4a**	60	98
2	H	4-CH_3	H	**4b**	60	90
3	H	3-CH_3	H	**4c**	60	81
4	H	4-Cl	H	**4d**	60	88
5	H	3-Cl	H	**4e**	60	88
6	H	4-Br	H	**4f**	60	93
7	H	3-Br	H	**4g**	60	83
8	H	2-Br	H	**4h**	60	74
9	H	4-F	H	**4i**	60	86
10	H	4-NO_2	H	**4j**	60	84
11	H	2-NO_2	H	**4k**	60	71
12	H	4-CN	H	**4l**	60	76
13	H	4-Pyridine	H	**4m**	60	68
14	H	H	4-CH_3	**4n**	60	93
15	H	H	4-OCH_3	**4o**	60	96
16	H	H	4-Br	**4p**	60	92
17	H	H	4-NO_2	**4q**	60	86
18	H	H	4-Pyridine	**4r**	60	77
19	4-Cl	H	H	**4s**	60	91
20	4-NO_2	H	H	**4t**	60	94

[a]Reaction conditions: Aldehyde (1 mmol), acetophenone (1 mmol) and aniline (1 mmol), $FeCl_3$ (10 mg), 1 h in solvent free neat condition at room temperature, [b]All are isolated products, [c]Isolated yield in percentage.

TABLE-4
COMPARISON OF CATALYTIC POTENTIAL OF $FeCl_3$ WITH OTHER CATALYSTS IN THE SYNTHESIS OF β-AMINO KETONE (**4a**)

Entry	Catalyst	Solvent	Catalyst load	Temp. (°C)	Time (h)	Yield (%)	Reuse	Ref.
1	Nano-ZnO	EtOH	5 mol %	27	6	92	–	[21]
2	Sulfonic acid supported on magnetic nanoparticle	Neat	2 mol%	27	4	95	5	[22]
3	Phenyl boronic acid	ACN	20 mol %	27	8	90	–	[23]
4	Citric acid	Water	10 mol%	27	10	80	–	[24]
5	CuO/PGO	Neat	2 mol %	27	0.15	95	5	[25]
6	$BiNO_3$	EtOH	5 mol %	27	4	90	–	[26]
7	SiO_2-$OAlCl_2$	EtOH	10 mol %	27	10	88	–	[27]
8	Boric acid	Glycerol	10 mol %	45	40	95	–	[28]
9	Ag_2CO_3	Toluene	5 mol %	27	4	85	–	[11]
10	$FeCl_3$	Neat	10 mol %	RT	1	98	–	Present work

TABLE-5
In vitro ANTIBACTERIAL ACTIVITY OF COMPOUND **4a**

Conc. (µg/mL)	Organisms/Zone of inhibition (mm)			
	S. aureus	*P. saeruginosa*	*B. subtilis*	*E. coli*
60	6	4	2	6
80	9	5	4	7
100	12	8	6	8
Std. amoxicillin (10 µL/disc)	14	11	10	12

TABLE-6
In vitro ANTIFUNGAL ACTIVITY OF COMPOUND **4a**

Conc. (µg/mL)	Organisms of zone of inhibition (mm)			
	C. albicans	*C. vulgaris*	*A. niger*	*A. flavus*
60	5	2	3	6
80	7	3	6	8
100	10	6	7	9
Std. fluconazole (10 µL/disc)	14	11	10	12

(9 mm). At the concentration of 80 µg/mL, compound **4a** exhibited the antifungal activity against all the tested fungi, but it was more susceptible against *C. albicans* and *A. flavus*. As the concentration of compound **4a** increased from 60-80 µg/mL, the inhibitory actions of compound **4a** increased towards all the tested strains.

Antioxidant activity: The antioxidant activity of compound **4a** and standard ascorbic acid against DPPH assay was tested with concentration ranging from 20 to 100 µg/mL. Based on Table-7 results, compound **4a** exhibit antioxidant activities at high concentration when compared with standard ascorbic acid. Compound **4a** has 72.32% antioxidant activity at 100 µg/mL, while ascorbic acid has 82.14% at the same concentration. The IC_{50} values of DPPH assay of compound **4a** was 32.90 µg/mL, While the standards antioxidant has an IC_{50} value of 21.75 µg/mL.

Anticancer activity: The synthesized β-amino ketone compound **4a** was also tested for its ability to kill the human breast cancer cell line MCF-7 using the MTT assay. Concentrations ranging from 2.5, 5, 7.5, 10 and 15 µg/mL were used to test the substances. Concentrations of compound **4a** showed the variable levels of cytotoxicity. It is displayed in Fig. 1 and demonstrates the prospective activities.

TABLE-7
ANTIOXIDANT ACTIVITY OF COMPOUND **4a**
BY DPPH ASSAY METHOD

Concentration (µg/mL)	Antioxidant activity DPPH (%)	
	Sample	Ascorbic acid
20	43.75	48.21
40	52.67	58.92
60	62.5	66.07
80	67.85	74.10
100	72.32	82.14
IC_{50} value	32.90	21.75

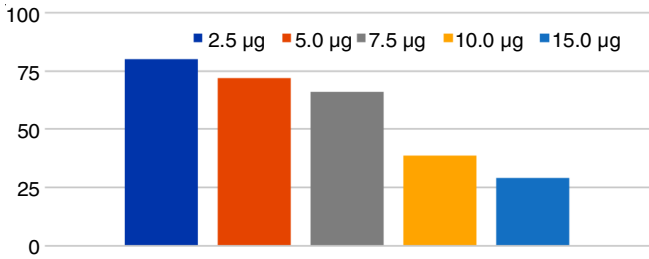


Fig. 1. Concentrations of the compound **4a** showed variable levels of cytotoxicity

Photomicrograph (10x) represents morphological changes in MCF-7 cells such as shrinkage, detachment, membrane blebbing and distorted shape induced by compound **4a** treatment (2.5, 5.0, 7.5, 10 and 15 µg/mL for 24 h) as compared with control (Fig. 2). Control showed normal intact cell morphology and their images were captured by light microscope.

Conclusion

A straightforward and eco-friendly process for synthesizing significant β-amino ketones without the use of solvents is described by employing catalytic quantities of $FeCl_3$ as a catalyst. Notably, the mild conditions were used to synthesize β-amino ketones with a dependable reaction time. This appro-

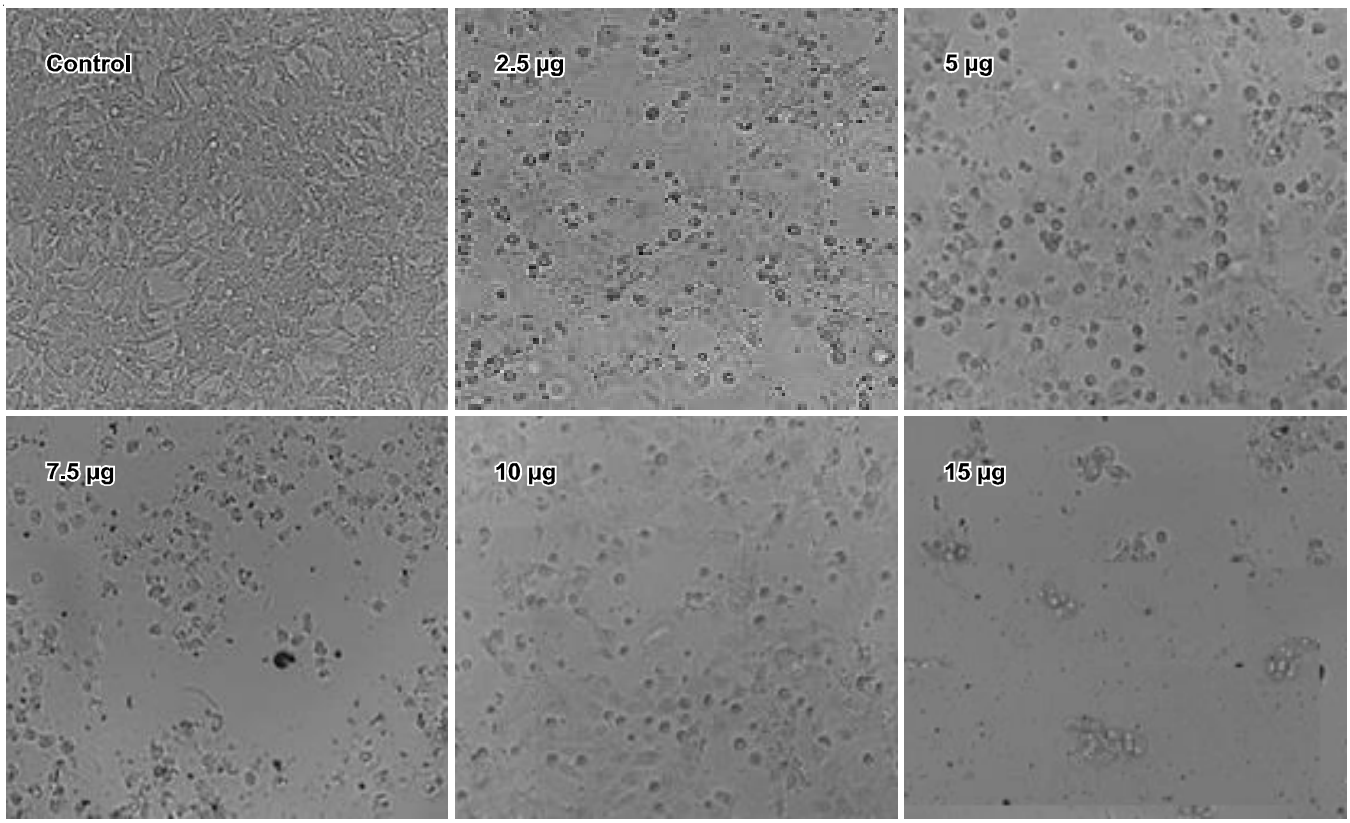


Fig. 2. Morphological changes in control and compound **4a** treated breast cancer MCF-7 cells for 24 h

ach exhibits the excellent functional group tolerance and efficiently removes bases and associated contaminants as well as chromatographic purification. The adaptability and efficiency of this approach were demonstrated by additional research on C-N and C-O bond forming processes. Inhibitory antibacterial action against *S. aureus* was demonstrated by compound **4a**. Among the other antifungal species, *C. albicans* had the strongest antifungal activity. The findings demonstrated that in comparison to conventional ascorbic acid, compound **4a** demonstrates strong antioxidant properties at high concentrations. Moreover, the morphological alterations in normal and compound **4a**-treated MCF-7 breast cancer cells during a 24 h period indicate the favourable results.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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