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Short communication

Synthesis and biological evaluation of aminoketones

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ABSTRACT

A three-component Mannich reaction of different ketones with aromatic aldehydes and different amines in microwave irradiation under solvent free condition afforded corresponding β-amino carbonyl compounds in excellent yields. This method proved as a novel and improved modification of the reported three-component Mannich reaction in terms of milder reaction conditions, reaction times, clean reaction profiles, very small quantity of catalyst and simple workup procedure. Newly synthesized β-amino-ketones were characterized by spectral studies. Structure of compound **4a** was also confirmed by single-crystal X-ray analysis. All the compounds were screened for their antimicrobial activity by MIC method. Few of the molecules were found to be biologically potent.

1. Introduction

Mannich reaction is one of the most important, carbon–carbon bond forming reaction in organic synthesis [1]. This reaction provides the formation of β-amino carbonyl compounds, which are important intermediates for the construction of various nitrogen-containing natural products and pharmaceuticals [2]. However, the drastic reaction conditions for the classical intermolecular Mannich reaction limits its synthetic usefulness. Therefore, numerous modifications of this reaction have been developed to overcome the drawbacks [1–3]. Many metal complexes have been used as Lewis acid catalysts to promote the reaction under anhydrous conditions [1–3], and few water-compatible Lewis acids were also reported [4]. However, these catalysts suffer from few disadvantages such as, large requirement of Lewis acid (usually more than 10 mol %), a long reaction time, and/or highly moisture sensitive reagents.

In the recent years, more efforts have been afforded for developing environmentally benign reactions and atom economic catalytic processes, that employ unmodified ketones, amines, and aldehydes for Mannich type reaction. Cerium chloride is used in many organic reactions as a catalyst [5] and as a reagent [6]. Since it has high solubility in water, it can be easily removed from the reaction by water wash. These advantages of cerium chloride prompted us to work on Mannich reaction, using cerium chloride as a catalyst.

N-Mannich bases have been widely applied as prodrugs of amine derivative drugs. The analogous C-Mannich bases (β-aminoketones) have received rather less attention probably because, they are not sufficiently susceptible to elimination at pHs encountered in vivo. Compounds, in which there is a thermodynamic advantage to elimination, may be an exception [7]. Further from the literature, it was observed that, β-aminoketones are biologically potent molecules such as, antibacterial, antifungal [8], analgesic, antiinflammatory [9] and as antivirals [10]. In view of these facts and in continuation of our research on pharmaceutically important heterocycles [11–14], we report herein a novel, rapid, and efficient three-component synthesis of β-aminoketones via a $CeCl_3$ (1 mol %) catalyzed one spot reaction in microwave, in 3 minutes duration. Moreover the product formed can be easily isolated just by pouring in to water.

2. Chemistry

In our initial experiments, substituted benzaldehyde **2**, substituted aniline **3**, and cyclohexanone **1** in acetonitrile were stirred for 4 h in the presence of catalytic amount (1 mol %) of $CeCl_3$ at room

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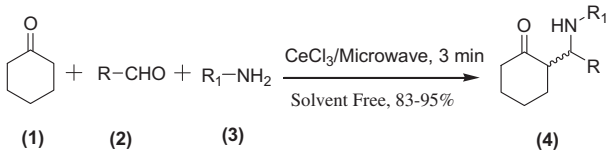

Scheme 1. Synthetic route for the three-component Mannich reaction.

temperature. Even after 4 h, no product was observed in mass analysis, further reaction mixture was heated to 80 °C for 8 h, which gave the corresponding β-aminoketones **4a** in very low yield (25%), with unreacted imine. Even after increasing the quantity of catalyst loading to 10 mol %, no any sign of improvement of the reaction. Further in our study we have used substituted benzaldehyde **2**, aniline **3**, cyclohexanone **1**, and 1 mol % of $CeCl_3$ in microwave tube, sonicated for 1 min, and irradiated in microwave for 3 min. Mass analysis of crude reaction mixture showed formation of only product with no starting material or side product (Scheme 1).

3. Results and discussion

As shown in Table 1, both the electron-deficient anilines and the electron-deficient benzaldehydes, electron-rich anilines and the electron-rich benzaldehydes afforded β-aminoesters **4** (**a**–**k**) in good to excellent yields (83–95%) (Table 1) of anti isomer, except in the compound **4(i)**, where 1:1 mixture of syn and anti isomers formed were confirmed by ^{13}C-NMR, where two distinct peaks for C=O is observed at 211 and 212. This is due to electron donating and electron withdrawing groups present in the same molecule. The anti and syn isomers were identified by the coupling constants (*J*) of the vicinal protons adjacent to C=O and NH in their ^{1}H-NMR spectra [15]. In general, the coupling constants for anti isomers are greater than that for syn isomers [16]. The ratio of the isomers were determined by integration of the corresponding peaks in ^{1}H-NMR spectra. As shown in Table 1, high anti selectivity was obtained in our three-component reaction. The anti-configuration of compound **4a** [17] was unambiguously established by X-ray crystallographic analysis (Fig. 1).

Further to our research, we have also successfully employed a convenient method for similar Mannich type reactions using heterocyclic aldehydes, heterocyclic amines and ketones at microwave conditions to give various β-aminoketones in excellent yields.

4. Antimicrobial studies

All the newly synthesized compounds were screened for their antibacterial activity. For this, *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* microorganisms were employed. Antimicrobial study was assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method [18]. Several colonies of *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* were picked off a fresh isolation plate and inoculated in corresponding tubes containing 5 mL of trypticase soya broth. The broth was incubated for 6 h at 37 °C until there was visible growth. Mc Farland No. 5 standard was prepared by adding 0.05 mL of 1% w/v $BaCl_2 \cdot 2H_2O$ in Phosphate Buffered saline (PBS) to 9.95 mL of 1% v/v H_2SO_4 in PBS. The growth of all the four cultures was adjusted to Mc Farland No. 5 turbidity standard using sterile PBS. This gives a 10^8 cfu/mL suspension. The working inoculums of aforementioned four different microorganisms containing 10^5 cfu/mL suspension was prepared by diluting the 10^8 cfu/mL suspension, 10^3 times in trypticase soya broth.

Table 1
Characterization of newly synthesized β-aminoketones (**4**).

S. No	R	R[1]	Yield (%)[a]	Anti/syn[b]
4a	Benzaldehyde	t-Butyl aniline	87	100:0
4b	4-Fluoro benzaldehyde	2,4-Difluoro Aniline	86	100:0
4c	2-Chloro benzaldehyde	4-Cyano Aniline	95	100:0
4d	2-Fluoro-5-methoxy benzaldehyde	2,4-Difluoro aniline	92	100:0
4e	2-Fluoro benzaldehyde	3,4-Difluoro aniline	88	100:0
4f	2-Allyloxy benzaldehyde	3-Fluoro aniline	85	100:0
4g	2-Hydroxy-3-methyl benzaldehyde	3-Methoxy aniline	93	100:0
4h	4-Ethyl benzaldehyde	3,4,5-Trifluoro aniline	95	100:0
4i	4-Ethyl benzaldehyde	4-Methyl-3 nitro aniline	90	60:40
4j	Benzofuran-2-aldehyde	Napthylamine	83	100:0
4k	Pyridine-4-carboxaldehyde	2-Methyl-5-aminoindole	88	100:0

[a] Isolated yield.
[b] Determined by ^{13}C-NMR.

4.1. Preparation of antimicrobial suspension (50 μg/mL)

Dissolved 0.5 mg of each compound in 10 mL of trypticase soya broth to get 50 μg/mL. This suspension was filter sterilized in syringe filters.

4.2. Preparation of dilutions

In all, for each of the 11 antimicrobial compounds and standard antimicrobial, i.e. Ceftriaxone, 24 tubes of 5 mL capacity were arranged in 4 rows with each row containing six tubes. Then 1.9 mL of trypticase soya broth was added in the first tube in each row and 1 mL in the remaining tubes. Now, 100 μl of filtered antimicrobial suspension was added to the first tube in each row and after mixing the content, 1 mL was serially transferred from these tubes to the second tube in each of the rows. The contents in the second tube of each of the rows were mixed and transferred to the third tube in each of the rows. This serial dilution was repeated till the sixth tube in each of the rows. This provided antimicrobial concentrations of 50, 25, 12.5, 6.25, 3.125, 1.6125 μg/mL in the first to sixth tube respectively in each row. Finally, 1 mL of 10^5 cfu/mL of *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* suspension were added to the first, second, third and fourth rows of tubes respectively. Along with the test samples and Ceftriaxone (standard), the inoculums control (without antimicrobial compound) and broth control (without antimicrobial compound and inoculum) were maintained. All the test sample and control tubes were then incubated for 16 h at 37 °C. The results are summarized in Table 2.

4.3. Interpretation

After incubation, the tubes showing no visible growth was considered to be representing the MIC. The details of results are furnished in Table 2. Inoculums control showed visible growth, where as the broth control showed no growth.

5. Conclusions

In summary, we have developed an efficient and simple method for the synthesis of β-amino carbonyl compounds via $CeCl_3$-catalyzed cascade reaction of anilines with various aromatic aldehydes and carbonyl compounds. The significant features of this procedure include: facile operation, cheap and readily available catalyst, high yields, reasonably good diastereo selectivities, very less reaction time.

Further antimicrobial screening showed that, most of the compounds are biologically potent and they showed significant antibacterial activity as compared to the standard drug Ceftriaxone, against the bacterial strains *S. aureus, B. subtilis, E. coli and*

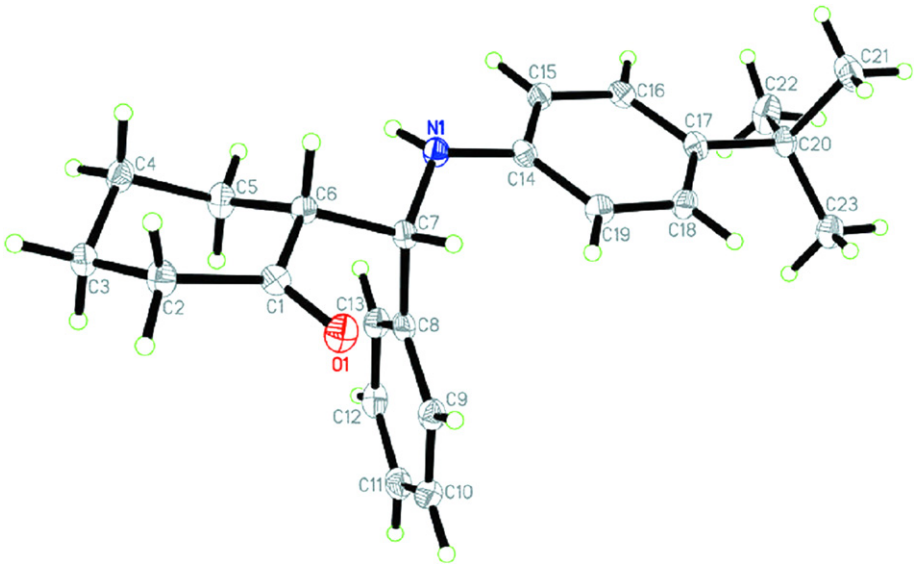

Fig. 1. Crystal structure of compound **4a**.

P. aeruginosa. Compounds **4b, 4c, 4d, 4e, 4g** and **4k** have showed excellent antimicrobial activity as that of the standard drug at same concentration. Compounds **4b, 4c, 4d,** and **4e** have halogen substitutions, while compound **4k** has pyridine and indole substitutions, which is accounted for the enhanced biological activity. Compound **4g** has methoxy substitution has also showed excellent activity. Compound **4a**, which has t-butyl substitution has showed poor antibacterial activity. Remaining compounds have showed moderate antimicrobial activity.

6. Experimental section

^{1}H-NMR and ^{13}C-NMR spectra were recorded on 400-MHz and 300-MHz Bruker spectrometers, respectively. Elemental analyses were performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on a Buchi Melting Point B-545 apparatus. All the compounds (**4a**–**k**) were synthesized in-house from the corresponding commercially available aldehydes, amines and ketone. The products were characterized by^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. The structure of compound **4a** was further confirmed by single-crystal X-ray analysis [17] on Bruker instrument.

Table 2
Antibacterial activity data in MIC (μg/mL).

Compound no.	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*
4a	6.250	6.250	12.5	6.250
4b	1.6125	1.6125	1.6125	1.6125
4c	3.125	1.6125	1.6125	1.6125
4d	3.125	1.6125	1.6125	1.6125
4e	3.125	1.6125	1.6125	1.6125
4f	6.250	3.125	3.125	6.250
4g	1.6125	1.6125	1.6125	1.6125
4h	12.5	12.5	12.5	12.5
4i	6.250	6.250	6.250	25
4j	3.125	3.125	1.6125	1.6125
4k	3.125	1.6125	1.6125	1.6125
Ceftriaxone (standard)	3.125	1.6125	1.6125	1.6125
Inoculum control	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations	Growth in all concentrations
Broth control	No growth	No growth	No growth	No growth

6.1. General procedure for synthesis of β-aminoketones (*4a*–*k*)

A mixture of aldehyde (1 mmol), amine (1 mmol), cyclohexanone (1 mmol) and cerium chloride (1 mol %) were taken in a sealed pressure regulation 10-mL pressurized vials with"snap-on" cap and sonicated for 2 min; resulting mixture was irradiated in the single-mode microwave synthesis system at 120 W power and 100 °C temperature for 3 min. Completion of reaction was confirmed by mass analysis. Reaction mixture was diluted with water and the solid separated was filtered, dried and recrystalised using ethylacetate to yield pure product **4(a–k).**

6.2. 2-((4-tert-Butylphenylamino)(phenyl) methyl) cyclohexanone *4a*

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.3$), Colourless solid. M.p. 154–156 °C.^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.41 (t, $J = 8$ Hz, 2H, Ar–H), 7.32 (m, 2H, Ar–H), 7.23 (m, 1H, Ar–H), 7.1 (t, $j = 8$ Hz, 2H, Ar–H), 6.5 (t, $J = 8.8$ Hz, 2H, Ar–H), 4.63 (d, $J = 7.2$ Hz, 1H, CH), 2.8 (m, 1H, CH), 2.3–2.5 (m, 2H, CH_2), 1.8 (m, 4H, $2CH_2$), 1.6 (m, 2H, CH_2), 1.23 (s, 9H, $3CH_3$).^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 212.8, 144.8, 142.0, 140.1, 128.4, 127.3, 127.1, 125.8, 113.2, 58.1, 57.5, 41.7, 33.7, 31.5, 31.1, 27.8, 23.5. IR (cm^{-1}) $1/\lambda = 3375$, 3025, 1760, 1619 cm^{-1}. LCMS (99.3%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 4.4 min, $m/z = 336.4$ $[M+1]^+$. Anal. Calcd. for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 82.30; H, 8.71; N, 4.20.

6.3. 2-((2,4-Difluorophenylamino)(4-fluorophenyl)methyl) cyclohexanone *4b*

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.4$), Colourless solid, M.p. 163–165 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.33 (m, 2H, Ar–H), 7.02 (m, 3H, Ar–H), 6.78 (d, $J = 8$ Hz, 1H, Ar–H), 6.35 (t, $J = 8.8$ Hz, 1H, Ar–H), 4.89 (bs, 1H, NH), 4.59 (t, $J = 6.8$ Hz, 1H, CH), 2.78 (m, 1H, CH), 2.3–2.5 (m, 2H, CH_2), 1.6–2.2 (m, 6H, $3CH_2$).^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 211.8, 163.1, 160.7, 152.5, 150.1, 136.5, 134.5, 128.9, 124.3, 121.2, 115.5, 113.6, 57.3, 42.3, 31.7, 28.5, 23.8. IR (cm^{-1}): $1/\lambda = 3375$, 3025, 1760, 1619 cm^{-1}. LCMS (98.0%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.22 min, $m/z = 334.0$ $[M+1]^+$. Anal.

Calcd. for $C_{19}H_{18}F_3NO$: C, 68.46; H, 5.44; N, 4.20. Found: C, 68.37; H, 5.35, N, 4.18.

6.4. 4-((2-Chlorophenyl) (2-oxocyclohexyl) methylamino) benzonitrile **4c**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.5$), Colourless solid, M.p. 225–227 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.19–7.37 (m, 6H, Ar–H), 6.6 (m, 1H, Ar–H), 6.57 (m, 1H, Ar–H), 5.7 (bs, 1H, NH), 5.36 (m, 1H, CH), 2.1–2.6 (m, 7H, $3CH_2$), 1.8 (m, 2H, CH_2).^{13}C-NMR(400 MHz, $CDCl_3$, 24 °C) δ (ppm): 211.8, 149.9, 137.3, 136.7, 135.5, 134.9, 133.6, 130.2, 128.2, 127.3, 126.4, 113.8, 100.2, 60.3, 56.1, 53.5, 27.6, 26.8, 22.6. IR (cm^{-1}): $1/\lambda = 3348$, 3028, 2243, 1730, 1629 cm^{-1}. LCMS (90.0%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 4.10 min, $m/z = 339.1$ $[M + 1]^+$. Anal. Calcd. for $C_{20}H_{19}ClN_2O$: C, 70.90; H, 5.65; N, 8.27. Found: C, 70.80; H, 5.68; N, 8.27.

6.5. 2-((2,4-Difluorophenylamino)(2-fluoro–methoxyphenyl) methyl) cyclohexanone **4d**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.3$), Colourless solid, M.p. 178–180 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 6.97 (m, 2H, Ar–H), 6.76 (m, 2H, Ar–H), 6.69 (m, 1H, Ar–H), 6.48 (m, 1H, Ar–H), 4.83 (bs, 2H, CH, NH), 3.72 (s, 3H, OCH3), 2.84 (m, 1H, CH), 2.43 (m, 2H, CH_2), 1.74–1.95 (m, 6H, $3CH_2$). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 212.2, 156.4, 155.9, 155.7, 154.10, 153.4, 152.5, 150.1, 132.0, 128.9, 115.8, 113.1, 110.6, 103.4, 56.155.5, 52.4, 42.2, 32.0, 28.1, 24.2. IR (cm^{-1}): $1/\lambda = 3364$, 3019, 17,410, 1614, 1474 cm^{-1}. LCMS (99.8%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.43 min, $m/z = 364.1$ $[M + 1]^+$. Anal. Calcd. for $C_{20}H_{20}F_3NO_2$: C, 66.11; H, 5.55N, 3.85. Found: C, 66.21; H, 5.45N, 3.88.

6.6. 2-((3,4-Difluorophenylamino)(2-fluorophenyl)methyl) cyclohexanone **4e**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.4$), Brown solid, M.p. 235–238 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (m, 2H, Ar–H), 7.03 (m, 3H, Ar–H), 6.89 (m, 1H, Ar–H), 6.21 (m, 2H, Ar–H), 4.76 (bs, 1H, NH), 4.46 (s, 1H, CH), 2.73 (m, 1H, CH), 2.3–2.44 (m, 2H, CH_2), 1.6–1.92 (m, 6H, $3CH_2$).^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 212.0, 162.7, 160.3, 151.5, 149.4, 143.8, 141.6, 136.4, 128.3, 116.9, 115.1, 108.5, 102.0, 57.8, 56.8, 41.8, 31.3, 27.5, 23.7. IR (cm^{-1}): $1/\lambda = 3323$, 3018, 1761, 1619, 1464 cm^{-1}. LCMS (98.3%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.22 min, $m/z = 334.0$ $[M + 1]^+$. Anal. Calcd. for $C_{19}H_{18}F_3NO$: C, 68.46; H, 5.44; N, 4.20. Found: C, 68.46; H, 5.48; N, 4.30.

6.7. 2-((3-Fluorophenylamino)(2-(allyloxy)phenyl)methyl) cyclohexanone **4f**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.2$), Brown solid, M.p. 175–177 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.37 (m, 1H, Ar–H), 7.20 (m, 1H, Ar–H), 6.8–6.96 (m, 3H, Ar–H), 6.12–6.35 (m, 4H, Ar–H, $CH_2 = CH$), 5.51 (d, $J = 8$ Hz, 1H, CH), 5.38 (m, 1H, CH), 5.11 (m, 1H, CH), 4.96 (bs, 1H, NH), 4.67 (s, 2H, OCH_2), 2.94 (m, 1H, CH), 2.34 (m, 2H, CH_2), 1.58–1.96 (m, 6H, $3CH_2$). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 213.0, 164.8, 162.4, 155.6, 148.9, 132.7, 129.6, 128.8, 127.7, 120.6, 117.1, 111.05, 109.0, 103.0, 99.6, 68.3, 55.3, 52.3, 41.6, 31.6, 27.7, 23.5. IR (cm^{-1}): $1/\lambda = 3326$, 3017, 1758, 1634, 1484 cm^{-1}. MS-$m/z = 354.1$ $[M + 1]^+$. anal. Calcd. for $C_{22}H_{24}FNO_2$: C, 74.76; H, 6.84; N, 3.96. Found: C, 74.76; H, 6.88; N, 3.96.

6.8. 2-((3-Methoxyphenylamino)(2-hydroxy-3-methylphenyl) methyl) cyclohexanone **4g**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.2$), White solid, M.p. 185–187 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.36 (d, 1H, $J = 12$ Hz, Ar–H), 7.20 (m, 2H, Ar–H), 6.71 (m, 2H, Ar–H), 6.35 (m, 1H, Ar–H,), 6.02 (s, 1H, Ar–H), 4.42 (bs, 1H, NH), 4.01 (s, 1H, CH), 3.75 (s, 3H, $-OCH_3$), 2.85 (m, 1H, CH), 2.11 (m, 4H, CH_3, CH), 1.47–1.96 (m, 6H, $3CH_2$). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 211.0, 16.0, 151.5, 144.6, 129.8, 128.3, 126.2, 120.0, 119.1, 114.5, 105.2, 99.84, 74.27, 54.93, 51.27, 38.92, 34.81, 26.2, 25.5, 22.8, 16.22. IR (cm^{-1}): $1/\lambda = 3356$, 3037, 1757, 1636, 1464 cm^{-1}. LCMS (96.5%, Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 4.0 min, $m/z = 322.0$ [M −18, −OH]). Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.34; H, 7.52; N, 4.18.

6.9. 2-((3,4,5-Trifluorophenylamino)(4-ethylphenyl)methyl) cyclohexanone **4h**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.6$), White solid, M.p. 168–170 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm):7.25 (m, 2H, Ar–H), 7.15 (m, 2H, Ar–H), 6.84 (m, 1H, Ar–H), 6.3 (m, 1H, Ar–H), 4.84 (bs, 1H, NH), 4.46 (s, 1H, CH), 2.77 (m, 1H, CH), 2.64 (m, 2H, CH_2), 2.36–2.46 (m, 2H, CH_2), 1.62–2.01 (m, 6H, $3CH_2$), 1.23 (t, $J = 4$ Hz, 3H, CH_3). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 212.1, 143.57, 137.6, 128.17, 127.05, 104.5, 101.8, 58.2, 57.2, 42.2, 31.7, 28.1, 27.9, 24.2, 15.2. IR (cm^{-1}): $1/\lambda = 3275$, 3063, 2925, 1724, 1630, 1544, 1461 cm^{-1}. LCMS (95.9%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75×4.6 mm 5 μm, RT = 3.90 min, $m/z = 362.1$ $[M + 1]^+$. Anal. Calcd. for $C_{21}H_{22}F_3NO$: C, 69.79; H, 6.14; N, 3.88. Found: C, 69.79; H, 6.14; N, 3.88.

6.10. 2-((4-Methyl-3-nitrophenylamino)(4-ethylphenyl)methyl) cyclohexanone **4i**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.2$), Yellow solid, M.p. 178–180 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 7.22 (m, 2H, Ar–H), 7.17 (m, 3H, Ar–H), 6.96 (m, 1H, Ar–H), 6.6 (m, 1H, Ar–H), 4.84 (bs, 1H, NH), 4.5–5.0 (m, 1H, CH, NH), 2.78 (m, 1H, CH), 2.6 (m, 2H,CH_2), 2.06–2.36 (m, 5H, CH_2, CH_3), 1.62–1.9 (m, 6H, $3CH_2$), 1.22 (t, $J = 4$ Hz, 3H, CH_3). ^{13}C-NMR (400 MHz, CDCl3, 24 °C) δ (ppm): 212.9, 211.3, 149.4, 146.4, 146.2, 143.4, 137.5, 128.1, 121.6, 118.6, 109.2, 58.07, 57.08, 56.2, 28.5, 26.8, 24.8, 23.8, 19.4, 15.2. IR (cm^{-1}): $1/\lambda = 3470$, 3367, 2955, 1719, 1544, 1461 cm^{-1}. LCMS (94.3%), Method; 0.1% HCOOH; ACN, Flow 1 mL/min, Column C 18 75 × 4.6 mm 5 μm, RT = 3.79 min, $m/z = 367.0$ $[M + 1]^+$. Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.99; H, 7.18; N, 7.65.

6.11. 2-((Benzofuran-2-yl)(naphthalen-1-ylamino)methyl) cyclohexanone **4j**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.2$), Colourless solid, M.p. 218–220 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 8.35 (m, 1H, Ar–H), 7.21–7.79 (m, 7H, Ar-H), 6.85 (m, 1H, Ar–H), 6.45 (m, 1H, Ar–H), 4.60 (d, $J = 8$ Hz, 1H, CH), 4.28 (bs, 1H, NH), 3.01 (m, 1H, CH), 1.5–2.59 (m, 8H, $4CH_2$). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 211.1, 158.0, 154.9, 140.0, 131.4, 128.7, 128.5, 124.2, 123.8, 122.5, 121.0, 120.9, 117.1, 113.7, 111.4, 104.5, 58.0, 53.10, 42.23, 35.01, 31.2, 26.3, 25.5, 21.10. IR (cm^{-1}): $1/\lambda = 3335$, 3067, 1619, 1461, 1254 cm^{-1}. $m/z = 370.1$ $[M + 1]^+$. Anal. Calcd. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.37; H, 6.27; N, 3.80.

6.12. 2-((2-Methyl-1H-indol-5-ylamino)(pyridin-4-yl)methyl) cyclohexanone **4k**

(TLC, Pet-ether/EtOAc, 1:1, $R_f = 0.2$), Colourless solid, M.p. 185–190 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 8.59 (s, 1H, Ar–H), 8.52 (s, 1H, Ar–H), 7.94 (s, 1H, Ar–H), 7.8 (m, 1H, Ar–H), 7.34 (m, 1H, Ar–H), 7.01 (d, $J = 12$ Hz, 1H, Ar–H), 6.3–6.6 (m, 3H, Ar–H). ^{13}C-NMR (400 MHz, $CDCl_3$, 24 °C) δ (ppm): 211.3, 149.8, 149.3, 138.3, 137.8, 136.4, 135.5, 135.3, 134.0, 125.5, 122.6, 100.6, 62.2, 40.10, 27.1, 26.5, 21.4, 13.78. IR (cm^{-1}): $1/\lambda = 3375$, 3050, 2925, 1689, 1461, 1254 cm^{-1}. MS, $m/z = 334.1$ $[M+1]^+$ 334. Anal. Calcd. for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.75; H, 6.98; N, 12.67.

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