Synthesis, Anti Cancer and Anti Fungal Studies of New Phenyl Ethylene Derivatives

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Synthesis of Phenyl ethylene derivatives (4a-4f) are reported in this communication. Products were characterized by 1HNMR, Carbon (13C) NMR and Mass spectral data. Synthesized compounds of 4a-4f were screened for anti cancer and anti fungal activities and their results are presented. The main intermediate (3) was prepared from 4-methoxy phenyl acetone (1) reacted with aqueous ethylamine and NaBH₄ to get the compound (2). Further dehydrohalogenation of (2) with 4-bromobutanol and potassium carbonate at 80°C resulted in compound (3) which on further dehydration with p-toluene sulfonic acid under reflux conditions gave 4a to 4f.

Keywords: Anti cancer; antifungal; Synthesis; 4-Methoxy phenyl acetone; derivatives and characterization.

1. INTRODUCTION

Phenyl ethylamine derivatives were found with very good biological activities viz., anticancer, antifungal. In addition some of the phenyl ethylamine derivatives also act as a musculotropic antispasmodic agent with a direct action on the smooth muscle of the gastrointestinal tract (GIT) especially phenyl ethyl amine derived esters are found to be inhibiting...
the peristaltic reflex of the guinea-Pigilem and inhibiting sphincter of odietc [1,2].

Besides the synthetic phenyl ethylamine and derivatives are also of great value in our daily life. Keeping in view, the author focused on the synthesis of phenyl ethylene derivatives. These scaffolds and analogs are being subjected to biological screenings like antifungal and anti cancer activities.

2. MATERIALS AND METHODS

Preparation of phenyl ethylene derivatives from 4-methoxy phenyl acetone (1) to final compounds (4a- 4f) used Chemicals, reagents and solvents that are LR grade. Data interpretation used SA-Varian 400MHz NMR for analysis of ¹H NMR and ¹³C NMR. Chemical shifts values are reported in δ(PPM) and duterated solvents are CDCl₃ and DMSO. Trimethyl silane (TMS) as a reference standard for NMR. The Multiplicity of spectra identified by following: Singlet (s), Doublet (d), Triplet (t), quarter (q), multiplet (m), broad (br), Doublet of doublet (dd).

The ESI/MS experiments were performed on a Velos Pro ion trap mass spectrometer from Thermo Scientific (San Jose, CA, U.S.A.). Elemental analysis for C, H and N used instrument vario EL.

Basic reaction completion in Laboratory identification used thin layer chromatography (TLC).

Performed anticancer studies in Stellixir Bio tech PVT Ltd, Bangalore, and Hela cell line and MCF7 from NCCS,PUNE. Anti fungal studies were performed at the Department of environmental science, GITAM institute of science, Visakhapatnam.

3. RESULTS AND DISCUSSION

The compounds are prepared by using the synthetic scheme shown below. The main intermediate (3) was prepared from 4-methoxy phenyl acetone (1) using reductive amination with aqueous ethylamine in the presence of Sodium borohydride to get the compound (2). Further dehydrohalogenation of (2) with 4-bromobutanol and potassium carbonate at 80°C resulted compound (3) which on further dehydration with p-toluene sulfonic acid under reflux conditions gave 4a to 4f. Products are characterized by ¹H NMR, ¹³C NMR and Mass spectral data [1-4].

3.1 Anti Cancer activity

3.1.1 MCF-7

MCF 7 is a human breast cancer cell line with estrogen, Progesterone and glucocorticoid receptors. It is useful for the in-vitro breast studies because they retained several ideal characteristics particular to mammary epithelium such as the processing of estrogen, in the form of Estradiol. It is the first human responding breast cancer cell line. It proves to be a suitable model cell line for breast cancer investigation worldwide. MCF 7 allows the researchers to use this cell line for bringing more light into breast cancer pathogenesis and treatment protocols through reliable in-vitro assay.

3.1.2 Hela cells

Refer to a line of cells belonging to a strain that has been continuously cultured since 1951. Compared to other human cells, Hela cell were the only survive in-vitro. Hela cells could be good acceptor for cross contamination with other cell line and possibility to lead number of misidentification cell line. Genome of Hela cell is highly unstable. In a lab setting hela cells was a first cell line that could be easily shared and multiplied.

Hele cell line was invented by Johns Hopkins. He is not expected any returns from the innovation of HeLa cells and he distributed HeLa cells to scientific research with free of cost. The very good contribution of Hela cell line in medical breakthrough. From research on the effects of zero gravity in outer space and the development of polio and COVID-19 vaccines, to the study of leukemia, the AIDS virus and cancer worldwide.

3.2 Antifungal Activity

Aspergillus candidus is a common contaminant of grain dust and causes respiratory disease in human. The species is widely distributed in nature and grows on vegetation in the later stages of decay. Aspergillus niger is fungi, it is also common contaminated foods grapes, apricots, onions, and peanuts. It cause a disease called Black mold. Aspergillus niger is less likely to cause human disease than some other Aspergillus species. In extremely rare instances, humans may become ill, but this is due to a serious lung disease.
3.2.1 Synthetic pathway for title compound (4a-4f) Scheme-1

![Scheme-1](image)

3.3 Experimental

3.3.1 Preparation of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine (2)

Taken 4-Methoxy phenyl acetone 1 (10.0 g, 0.16 mol) in methanol (60.0 mL, 6.0 t), at room temperature, charged slowly the aqueous ethylamine (25.0 mL, 2.5 t) into the mass then the reaction mass was cooled to -3±2°C. At the same temperature slowly added sodium borohydride portion wise (3.0 g, 0.01 mol). Then the reaction mass was maintained for 1hr. Charged water (200.0 mL) and toluene (50.0 mL) into reaction mass, stirred the reaction mass for 5 to 10 min and separated the toluene layer and water layer. After distillation of toluene layer got the required N-Ethyl-1-(4-methoxyphenyl) propan-2-amine 2 was obtained.

\[ \text{H NMR (DMSO d_6, 400 MHz): } \delta 7.08-7.06 (d, 2H), 6.82-6.80 (d, 2H), 4.51-4.49 (m, 1H), 3.70 (s, 3H), 3.36 (t, 3H), 2.88-2.83 (m, 1H), 2.73-2.68 (m, 1H), 2.43-2.29 (m, 4H), 1.38-1.37 (m, 4H), 0.95 (t, 3H), 0.83-0.82 (d, 3H) \]

Mass (M+H): 194.2, Weight: 8.0g Purity: NLT 95.0.

3.3.2 Preparation of 4-(N-Ethyl-N-(1-(4-methoxyphenyl) propan-2-yl) amino)butan-1-ol (3)

Stirred a solution of N-Ethyl-1-(4-methoxyphenyl) propan-2-amine (2) 7.5 g, 4-bromobutanol (22.0 g) in toluene (30.0 mL). Reaction mass temperature was raised to 80±5°C for 24 to 30 hrs. After completion of reaction, cooled the reaction mass to 30±5°C then charged 10 mL of water into the mass and stirred for 10 min. Separated the toluene layer and aqueous layer followed by distillation of toluene layer to get the 4-(N-Ethyl-N-(1-(4-methoxyphenyl) propan-2-yl)amino)butan-1-ol.

\[ \text{H NMR (DMSO d_6, 400 MHz): } \delta 7.08-7.06 (d, 2H), 6.82-6.80 (d, 2H), 4.51-4.49 (m, 1H), 3.70 (s, 3H), 3.36 (t, 3H), 2.88-2.83 (m, 1H), 2.73-2.68 (m, 1H), 2.43-2.29 (m, 4H), 1.38-1.37 (m, 4H), 0.95 (t, 3H), 0.83-0.82 (d, 3H) \]

Mass (M+H): 266.2

3.3.3 Process for the preparation of title compounds 4(a-h)

Carried out the dehydration of compound 4 and corresponding acid in presence of PTSA and toluene at 105 to 115 °C for 22±5 h. after maintenance cool the reaction mass and charge water into the reaction mass and stir for 10 min and separated the organic layer and distilled the organic layer(toluene) completely. The obtained crude was purified with column chromatography by using 5-8 % of Dichloromethane in Ethyl acetate.

3.3.4 4-(Ethyl(1-(4-methoxyphenyl)propan-2-yl)amino)butyl 3,4-dimethoxybenzoate hydrochloride (4a)

\[ \text{H NMR (CDCl_3, 400 MHz): } \delta 12.1-12.2 (brs, 1H), 7.68 (dd, 1H J 1.6), 7.53 (d, 1H J 1.6), 7.15 (d,}
1H J 0.8), 6.88 (d, 1H J 8.4), 6.83 (d, 2H, J 8.4), 4.37 (t, 2H J 6.4), 3.93 (s, 6H), 3.78 (s, 3H), 3.56 (d, 2H J 10.8), 3.22-3.08 (m, 4H), 2.54 (t, 1H), 2.14-2.13 (m, 2H), 1.89 (t, 2H), 1.56-1.54 (m, 3H), 1.24 (d, 3H J 6)

$^{13}$C NMR: 59.88, 12.02, 21.19, 26.20, 36.20, 44.63, 45.95, 54.89, 55.72, 59.43, 63.07, 110.45, 111.62, 113.87, 122.02, 123.30, 127.68, 129.77, 148.31, 152.78, 158.40, 165.91.

Mass: M.Wt: 429.2 (M+H: 430.2)

3.3.5 4-(Ethyl(1-(4-methoxyphenyl)propan-2-yl)amino)butyl thiophene-2-carboxylate (4b)

$^{1}$H NMR: (CDCl$_3$ 400 MHz): δ 7.83 (d, 1H J 7.2), 7.45-7.41 (m, 2H), 7.34-7.32 (m, 1H), 7.13 (d, 2H J 8.4), 6.82 (d, 2H J 8.4), 4.38 (t, 2H J 6), 3.77 (s, 3H), 3.49-3.37 (m, 2H), 3.13-2.92 (m, 4H), 2.54-2.48 (m, 1H), 2.06-2.00 (m, 2H), 1.90-1.85 (m, 2H), 1.42 (t, 3H J 8), 1.16 (d, 2H J 8).

Mass: M.Wt: 375 (M+1: 376)

3.3.6 4-(Ethyl(1-(4-methoxyphenyl)propan-2-yl)amino)butyl 2-chlorobenzoate (4c)

$^{1}$H NMR (CDCl$_3$ 400 MHz): δ 88.04 (dd, 2H J 8), 7.55 (t, 1H), 7.43 (t, 2H), 7.06 (d, 2H J 8), 6.79 (d, 2H J 8), 4.29 (t, 2H), 3.76 (s, 3H), 2.97-2.92 (m, 1H), 2.85-2.80 (m, 1H), 2.60-2.47 (m, 4H), 2.37-2.34 (m, 1H), 1.80-1.69 (m, 2H), 1.59-1.53 (m, 2H), 1.051 (t, 3H J 8), 0.91 (d, 3H J 8).

Mass: M.Wt: 404 (M+2: 406)

3.3.7 4-(Ethyl(1-(4-methoxyphenyl)propan-2-yl)amino)butyl benzoate(4d)

$^{1}$H NMR, (CDCl$_3$, 400 MHz): δ 57.91 (d, 1H J 8), 7.23-7.22 (m, 1H), 7.13-7.06 (m, 2H), 6.83-6.79 (m, 3H), 6.73-6.71 (m, 1H), 4.38 (t, 1H), 3.75-3.70 (m, 4H), 3.61-3.46 (m, 4H), 3.12-3.00 (m, 2H), 2.60-2.49 (m, 1H), 2.06-2.01 (m, 3H), 1.42 (t, 3H), 1.25-1.016 (m, 3H).

Mass: M.Wt: 369 (M+1: 370)

3.3.8 4-(Ethyl(1-(4-methoxyphenyl)propan-2-yl)amino)butyl 2-bromobenzoate (4e)

$^{1}$H NMR (CDCl$_3$, 400 MHz): δ 87.80 (dd, 1H J 2), 7.65 (dd, 1H J 1.2), 7.40-7.28 (m, 2H), 7.14 (d, 2H), 6.83 (d, 2H), 4.4 (t, 2H), 3.78 (s, 3H), 3.56-3.51 (m, 2H), 3.23-2.96 (m, 4H), 2.57-2.51 (m, 1H), 2.18-2.06 (m, 2H), 1.92-1.877 (m, 2H), 1.48 (t, 3H), 1.21 (d, 3H).

$^{13}$C NMR, CDC13: δ 10.43, 12.55, 21.81, 26.26, 36.73, 45.37, 49.40, 55.16, 59.45, 64.41, 114.09, 121.27, 127.25, 128.33, 130.20, 131.27, 132.03, 132.57, 134.14, 158.56, 166.14

Mass: M.Wt: 448 (M+2: 450)

3.3.9 4-(ethylv(1-(4-methoxyphenyl)propan-2-yl)amino)butyl 2-bromo-6-methoxybenzoxide (4f)

$^{1}$H NMR (CDCl$_3$, 400 MHz): δ 87.51 (d, 1H J 8), 7.29 (d, 1H), 7.13 (d, 2H), 6.90-6.87 (m, 1H), 6.83-6.81 (d, 2H J 0.8), 4.38 (t, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.52-3.49 (m, 1H), 3.41-3.38 (dd, 1H), 3.19-2.96 (m, 4H), 2.55-2.49 (m, 1H), 2.10-2.03 (m, 2H), 1.91-1.86 (m, 2H), 1.44 (t, 3H), 1.18-1.17 (d, 3H).

$^{13}$C NMR, CDC13: δ 10.72, 12.67, 22.10, 26.25, 36.89, 45.24, 49.39, 55.14, 55.61, 59.59, 64.65, 111.43, 114.03, 114.38, 116.21, 118.81, 128.71, 130.19, 132.76, 134.85, 158.47, 158.52, 166.04

Mass: 478 (M+2: 480)

3.4 Anti Cancer Activity

Calculated IC 50 values of the anti Cancer activity of newly synthesized phenyl ethylene derivatives against MCF7 and HeLa cell line are tabulated in Table 1. All the compounds are found to be showing good anti cancer activity. Some of the compounds 4d, 4e, and 4f showed high potential and remaining compounds showed moderate potential values.

### Table1. List of compounds

| S.No. | Compound name | Hela IC 50 (µG/mL) | MCF7 IC 50 (µG/mL) |
|-------|---------------|-------------------|-------------------|
| 1     | 4a            | 29.51             | 25.97             |
| 2     | 4b            | 38.07             | 22.41             |
| 3     | 4c            | 28.7              | 31.05             |
| 4     | 4d            | 44.5              | 37.18             |
| 5     | 4e            | 46.5              | 40.18             |
| 6     | 4f            | 67.1              | 55.01             |

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Table 2. Fungal species zone of inhibition

| S.No | Name of the compound | Aspergillus niger | Aspergillus candidus |
|------|----------------------|------------------|---------------------|
| 1    | 4a                   | 25               | 28                  |
| 2    | 4b                   | 12               | 14                  |
| 3    | 4c                   | 9                | 8                   |
| 4    | 4d                   | 10               | 8                   |
| 5    | 4e                   | 18               | 25                  |
| 6    | 4f                   | 14               | 12                  |

Table 3. Report On Antibiotic Assay With Fungi

| S.No | Sample name | Growth of Inhibition | Photo |
|------|-------------|----------------------|-------|
| 1.   | 4a, 4b, 4c  | All have shown the zone of inhibition but 4a has shown very high zone of inhibition to *Aspergillus niger* and *Aspergillus candidus* | ![Photo](image1) |
| 2.   | 4d, 4e, 4f | All have shown the zone of inhibition but 4e has shown very high zone of inhibition to *Aspergillus niger* and *Aspergillus candidus* | ![Photo](image2) |

3.5 Antifungal Activity

The antifungal activities with zone of inhibition of all the newly synthesized 2-phenyl ethylene derivatives were evaluated in vitro against a wide variety of fungal species such as *Aspergillus niger* and *Aspergillus candidus*. All the compounds exhibited antifungal activity less than the reference standard *Pencillin G*. Compound 4a and 4e exhibited good antifungal activity than remaining compounds [5-8].

4. CONCLUSION

In the present study, we have reported the synthesis of 4-[Ethyl(4-methoxy-a-methyl phenethyl)amino]butyl veratrate and their novel derivatives were found to be broad spectrum anticancer and antifungal agents. Results suggest the utility of the these novel series against cancer and fungal diseases. Still some more studies are in progress to optimize these molecules to get the potent inhibitor, and will report in the due course.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nandini R. pai, Deepnandan S. Dubhashi. Synthesis and Preliminary pharmacological evolution of veratric acid ester 4-[ethyl-[2-4-methoxy phenyl-1-methyl ethyl] amino] butan-1-ol derivatives. Der Pharma Chemical. 2010;2(2):366-378.
2. Philips NV. ‘GloeilampenFabrie-Ken. Improvements in or relating to the production of esterified amino-alcohols. Patent No. GB 1009082A
3. Mantena Venkata Rama Raju, Mantena Ashok Srinivasa Raju, Mantena Anand, Vamsi Krishna G, Phani Kumar VSRN, Suraparaju Raghu Ram, Satyanarayana Y, Sateesh CHLD, Srinivasa Rao D, Chandra Mouli K, Ramakrishnam Raju A, Seshagiri Rao S. Process for the
preparation of Mebeverine hydrochloride. Ind Patent. 2018;410:23171.

4. Palaniappan S, Ram MS. Esterification of carboxylic acids with alcohols catalyzed by polyaniline salts. Green Chemistry. 2002;4(1):53–55.

5. Seham S, Abdulhady1*, Khaled M Hosny Ibrahim2. Preparation and evaluation of Mebeverine hydrochloride as mucoadhesive buccal tablet for local anesthesia. Tropical Journal of Pharmaceutical Research. 2017; 16(8):1805-1812.

6. Vijai Varma Pothuri PVS, Machi Raju, Samba Siva Rao V. Synthesis and biological activity some novel derivatives. Russian Journal of General Chemistry. 2020;90(5):889-894.

7. Prathap M, Gulshan MD, Rama Rao N, Sathish Kumar M. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2016;7(1): 1242-1252.

8. Souri E, Negahban A, Adhdami, Adib N. Research in Pharmaceutical Science. 2014;9(3):199-206.

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