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Convenient Synthesis and Structural Characterization of a Series of Methyl 4-[2-(cyclized amino)ethoxy]benzoate Esters as Key Intermediates in Synthesis of Selective Estrogen Receptor Modulators

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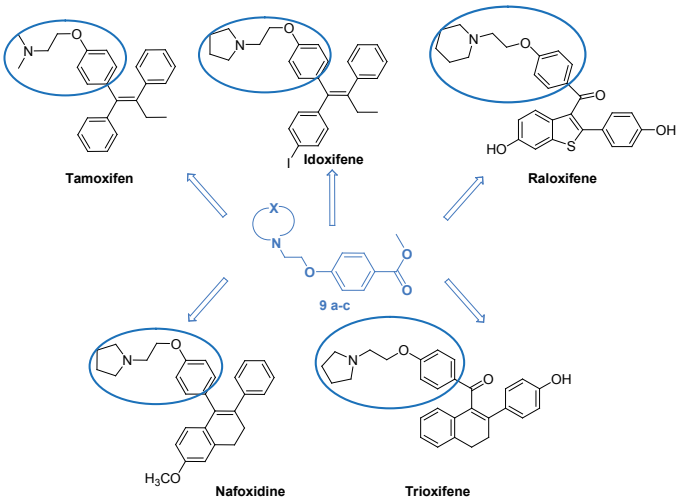
Abstract

Estrogen receptors, the important selective targets in management of serious aspects in women health challenging issues, guided the scope of drug discovery towards developing new entities treating osteoporosis and breast cancer. Tracing aminoethoxyphenyl pharmacophoric essential antagonistic group, abundantly present in Selective Estrogen Receptors Modulators (SERMs), directed the authors to study and explore the prospect to synthesize and exclusively characterize a series of methyl 4-[2-(cyclized amino)ethoxy] benzoate esters 9a-c rather than their reported free acids as fundamental and convenient key intermediates synthesizing potential SERMs. This paper describes synthesis and spectral characterization of these esters. The relative significant ^{1}H-NMR shifts related to synthesized derivatives were illustrated. ^{13}C-NMR data were particularly discussed. Moreover, molecular ion peaks and different fragmentation patterns in mass spectral analysis were demonstrated. Furthermore, retention time of different derivatives at specified conditions using gas chromatography-mass spectrometry was assigned. Purity of compounds was confirmed by elemental analysis; found data were within ± 0.4% of the theoretical values.



Keywords: Aminoethoxybenzoate esters; Aminoethoxyphenyl methanone; Selective estrogen receptor modulators; Osteoporosis; Breast cancer; Women health

Introduction

The process of changing problematic current scenarios in women health issues acquired a great significance in last decade, where there is a global debate on actual fulfilling of women health needs, especially post-menopausal women, by general health care provision. Researchers exert endless efforts in design, development and optimization of millions of novel entities related to women common diseases and conditions, in a collaborative manner from all relevant fields including, medicinal and synthetic organic chemistry along with advances in receptors physiology [1].

17β-estradiol I, (Figure 1) is a steroid estrogenic hormone having a critical role in female reproductive functions along with growth, maintenance and homeostasis of several tissues including skeletal, cardiovascular and nervous systems. Estrogenic responses are typically mediated through binding to specific biological targets which are ligand-regulated nuclear receptors namely estrogen receptors (ERs). ERs exist in two different isoforms: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) [2]. These isoforms differ in size, expression and distribution among different tissues [3]. ERα was reported to possess a proliferative role, while ERβ has an anti-proliferative action [4].

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Unfortunately, ERβ expression declines during cancer progression in invasive breast carcinoma as compared to normal mammary cells [5].

Estrogen deficiency in postmenopausal women reduces bone mineral density (BMD), which leads to increased risk of fractures [6]. This deficiency is considered as an important contributor to postmenopausal osteoporosis [7]. Thus, it is possible to inhibit bone loss in postmenopausal women by estrogen administration as hormonal replacement therapy (HRT) [6]. However, this therapy can augment the risk of hormone dependent uterine and breast cancer [2]. The unfavorable effects of traditional HRT inspired a deep follow up to build up selective estrogen receptor modulators, which can be received for longer time without emerging serious adverse effects [8]. Selective Estrogen Receptor Modulators (SERMs), including Tamoxifen II, Idoxifene III, Raloxifene, IV, Nafoxidine, V, Trioxifene IV (Figure 2), and many others, displayed mixed estrogenic and anti-estrogenic actions depending on tissues type.

The anti-estrogenic profile of tamoxifen in breast cells succeeded to prevent ER-positive breast cancer recurrences [8]. Tamoxifen decreased recurrence 10-year risk by about one-half and death risk by almost one-third [9]. Clinical trials on breast cancer showed that the use of tamoxifen reduced both contra-lateral breast cancer and breast cancer recurrences by 40% to 50%. The efficacy of tamoxifen was also studied in Phase III trials and it is found to reduce the overall incidence of breast cancer between 16% and 49% and that of ER-positive breast cancer between 31% and 69% [4]. As well, tamoxifen induces a favorable estrogenic action in bones to inhibit osteoporosis [8]. On the other hand, its agonistic activity in uterus can cause or increase endometrial cancer risk [8]. Compared to tamoxifen action on bones, raloxifene plays a superior role in osteoporosis prevention by having greater agonistic effect at the level of bones but antagonistic activity in breast thus prevents tumor growth. Yet, it is not linked with an increased risk of uterine cancer [8]. Clinical studies have verified that raloxifene anti-

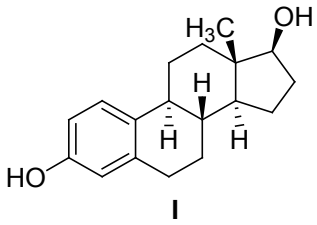


Figure 1: Structure of 17β-estradiol (I).

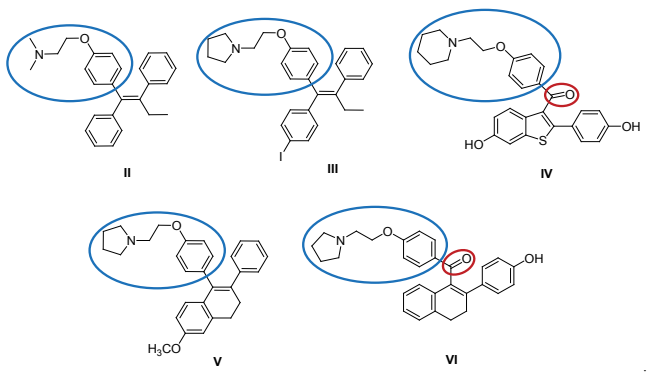


Figure 2: Significance of aminoethoxyphenyl basic side chain in different SERMs.

osteoporotic effect is related to its ability to modulate bone turnover [10]. Three clinical trials MORE, CORE, and RUTH, have tackled the effect of raloxifene on bone health. Raloxifene showed 30% and 55% reduction in vertebral fracture in women with and without fractures in 3 years, respectively [11]. Realizing actual value of SERMs in overall management of women health problems led researchers to focus on drug optimization and derivatization of such promising molecules [1].

The structural core of SERMs generally integrates a non-steroidal poly-aromatic phenolic unit, along with a basic tertiary amine ether side chain [12]. Structure activity relationship (SAR) studies emphasized on the importance of basic side chain in antagonistic activity of SERMs. This aminoethoxy phenyl side chain, linked to a methanone group in some analogs (Figure 2), is an attractive target for structural modification and enhancement [12].

At molecular level, both estradiol and SERMs bind to estrogen receptor by fitting into hydrophobic pocket of ligand binding domain (LBD). Analyzing the protein-ligand complexes in two dimensions of reported crystalline structures of ERα bound to 17β-Estradiol (1ERE) and Raloxifene (1ERR) [13], they revealed the importance of phenolic hydroxyl groups in estradiol (a) and that of benzothiophene part in raloxifene (b) in binding to Glu353 and Arg394 amino acids located in LBD (Figure 3a). Whereas antiestrogenic amino side chain of raloxifene (Figure 3b) interacts with aspartate 351, leading to carboxylic acid charge shielding and prevention of helix 12 reorientation important for LBD sealing [14]. This helix disposition is a common feature for all anti-estrogens having a bulky side chain [13]. The pharmacodynamic response of estrogens and SERMs fitting either ERα and/or ERβ receptor in relation to their organ distribution and different contributions is difficult to establish and still not clearly investigated [5].

Many researchers have examined the influence of a variety of side chain derivatives on promising candidates regarding their improved agonist-antagonist estrogenic activity and their relative selectivity towards various tissues [15,16]. Interestingly, some synthesized derivatives showed ascending antagonistic potencies as we are stepping from acyclic amine to cyclic analogs including pyrrolidino and piperidinoethoxy side chains [14].

Different methods and strategies were adopted for synthesis of SERM analogs. A direct Friedel-Crafts acylation of a 2-arylbenzothiophene 1 using 4-[2-(substituted amino)ethoxy]benzoyl chloride, 2, has been reported for the synthesis of several raloxifene analogs with different aryl and amino functionalities as outlined in Figure 4 [12,17,18].

Easy and applicable introduction of aminoethoxyphenylmethanone basic side chain using different benzoyl chloride intermediates onto benzothiophene core structure spots the light on the importance of these intermediates in synthetic process of SERM analogs. Acid chlorides are usually synthesized by replacing the hydroxyl group of corresponding carboxylic acid, hydrolyzed from corresponding ester, by treating it with chloride using thionyl chloride ($SOCl_2$) or other reagents [19].

Moreover, the synthesis of some pyran-containing SERMs, reported the use of benzoic acid derivatives as key intermediates in the heterocyclic ring closure which is an essential step in the overall synthesis. Dibenzopyranone derivatives 5 were synthesized in a good yield by resorcinol condensation with substituted 5-methoxy-2-bromo benzoic acids 4 (Figure 5) [20]. Furthermore, another research group reported the synthesis of 2, 3-Diaryl-1-benzopyran analog 6 using the acid chloride as a source of carbon needed for pyran ring closure. This was followed by alkylation with 2-pyrrolidinoethyl chloride as addressed in Figure 6 [21].

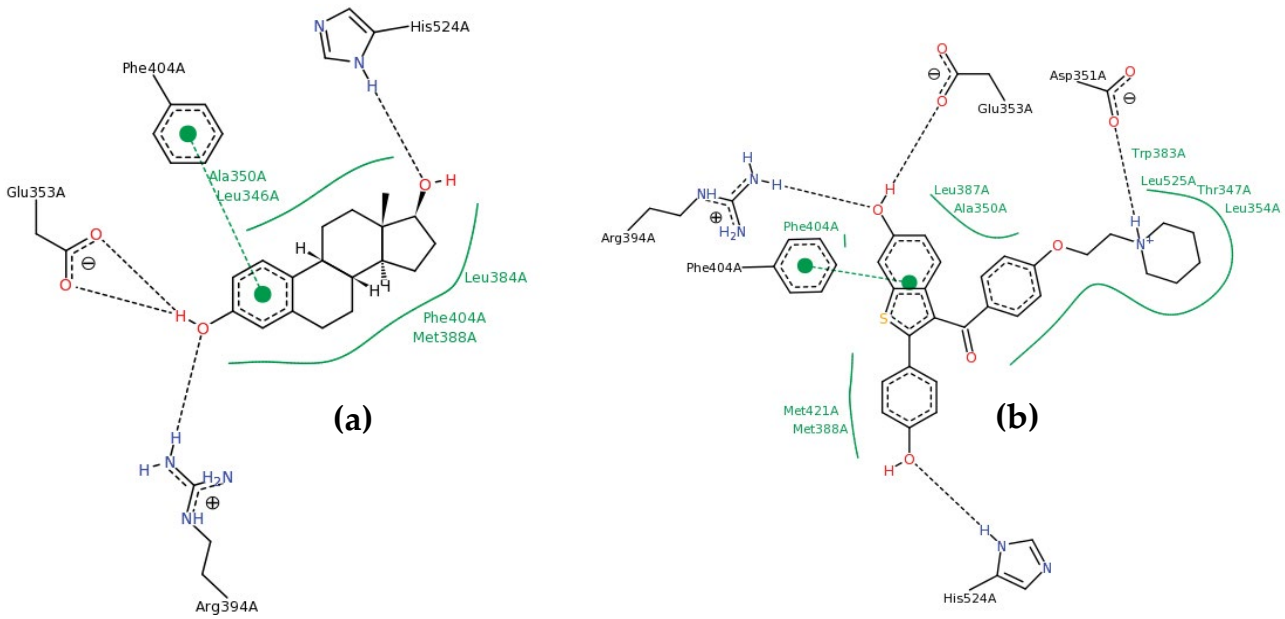


Figure 3: Binding of 17β-Estradiol (a) and Raloxifene (b) to human ERα. Black dashed lines indicate hydrogen bonds. Green solid line show hydrophobic interactions and green dashed lines show π-π and π-cation interactions.

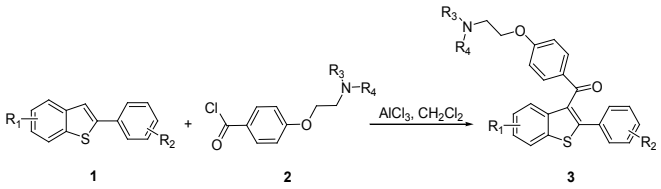


Figure 4: Friedel-Crafts acylation approach in raloxifene analogs synthesis.

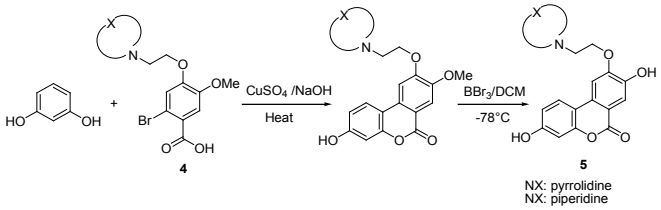


Figure 5: Synthesis of dibenzopyranone derivatives as SERMs.

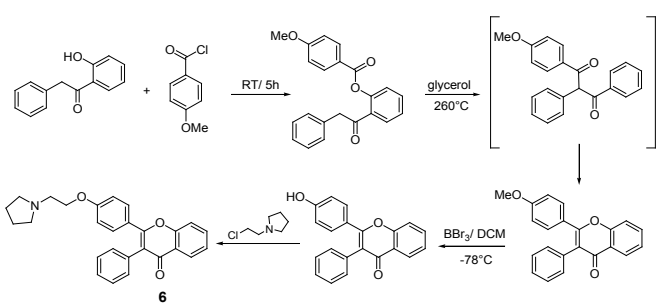


Figure 6: Synthesis of 2,3-Diaryl-1-benzopyran analogs as SERMs.

Owing to huge importance of SERMs in managing several diseases, derivatization process to produce more promising analogs is in accelerating motion. Furthermore, understanding the importance of using purified characterized esters as alternate intermediates in synthesis of potential SERMs scaffolds, in an absence of sufficient literature information describing and characterizing relevant esters, instead, reported esters were used without purification to produce corresponding acids only characterized by ^{1}H-NMR, IR and UV [18]. Here in, we aimed at the synthesis and full characterization of methyl 4-[2-(cyclized amino)ethoxy]benzoate esters as key intermediates important for synthetic approaches incorporating the aminoethoxy phenyl side chain antagonistic pharmacophore. Taking into consideration the interesting action of cyclic amines, target intermediates amino group will be presented as piperidino, pyrrolidino and morpholino derivatives.

Materials and Methods

All solvents and reagents were purchased from commercial suppliers and were dried and purified, when necessary, by standard techniques. The follow-up of reactions and checking the homogeneity of compounds were performed using Thin Layer Chromatography (TLC) on DCMikrokarten Polygram SIL G/UV254, of thickness: 0.25 mm from the Macherey-Nagel Firm, Duren. Column Chromatography was carried out using Silica gel, ICN Silica 100-200 active 60A, Silica gel 60 (particle size 0.015-0.040 mm), Merck. Magnesium sulfate was used for drying of organic phases. ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Brucker spectrometer Avance spectrometer (300 MHz), at the Micro Analytical Unit, faculty of science, Beirut Arabic University. Mass spectra of synthesized compounds were recorded on Shimadzu QP (70 eV) at Micro Analytical Center, Cairo University. Gas chromatography analysis was recorded using Agilent GC-MS (El), faculty of pharmacy, Beirut Arabic University. The microanalysis was performed at Microanalytical Laboratory, National Research Center, Cairo, Egypt.

General procedure for the synthesis of methyl 4-[2-(cyclized amino)ethoxy]benzoate esters 9a-c

To a mixture of 4 ml anhydrous DMF and 1.13 g of finely grinded anhydrous K_2CO_3, 0.5 g of methyl 4-hydroxybenzoate was added and heated to 100°C. Gradual addition of 0.68 g of appropriate N-(2-chloroethyl)amine hydrochloride 8a-c was done over 10 min. The reaction was allowed to proceed for 1.5 hour at 100°C. Filtration was carried out and the filtrate was evaporated to remove most of DMF to provide an oily brown residue. The precipitate from filtration was dissolved in 10 ml of water and extracted twice with 5 ml of ethylacetate. The brown oil was dissolved by the resulted ethylacetate extracts which was then washed with several portions of aqueous NaCl solution. The ethylacetate solution was dried and evaporated to yield brown oil, which gave single spot on TLC analysis using ethylacetate for elution. The product was purified on silica column using n-hexane: ethylacetate (9:1) as eluting system.

Methyl 4-[2-(1-pyrrolinyl)ethoxy]benzoate ester (9a): Yield 65%; ^{1}H-NMR (300 Hz, DCM); δ 7.99 (d, 2H, J=9 Hz, phenyl $C_{2,6}$-H), 6.96 (d, 2H, J=9 Hz, phenyl $C_{3,5}$-H), 4.13 (t, 2H, NCH_2CH_2O), 3.88 (s, 3H, CH_3), 2.93 (t, 2H, NCH_2CH_2O), 2.63 (t, 4H, pyrrolidine $C_{2,5}$-H), 1.81 (m, 4H, pyrrolidine $C_{3,4}$-H); ^{13}C-NMR (300 Hz, DCM); 166.9 (*C*OO-CH_3), 163.1 (phenyl C_4), 131.7 (phenyl C_2 and C_6), 123 (phenyl C_1), 114.5 (phenyl C_3 and C_5), 67.6 (NCH_2CH_2O), 55.1 (pyrrolidine C_2 and C_5), 54.9 (NCH_2CH_2O), 52 (CH_3), 23.9 (pyrrolidine C_3 and C_4); MS (EI, 70ev) m/z (%): 250 (M+1,12.39), 235 (10.19), 221 (11.88), 202 (10.53), 164 (13.41), 126 (12.9), 121 (14.77), 84 (100), 77 (5.94). GC-MS (EI), rt=36.526 min, *m/z* (%): 250 [M+1]. Anal. Calcd. for $C_{14}H_{19}NO_3$ (249.31): C, 67.45 ; H, 7.68 ; N, 5.62; Found: C, 67.12; H, 7.43; N, 5.86.

Methyl 4-[2-(1-piperidinyl)ethoxy]benzoate ester (9b): Yield 68%; ^{1}H-NMR (300 Hz, DCM); δ 7.98 (d, 2H, J=6.9 Hz, phenyl $C_{2,6}$-H), 6.95 (d, 2H, J=6.9 Hz, phenyl $C_{3,5}$-H), 4.15 (t, 2H, NCH_2CH_2O), 3.88 (s, 3H, CH_3), 2.77 (t, 2H, NCH_2CH_2O), 2.51 (t, 4H, piperidine $C_{2,6}$-H), 1.61 (m, 4H, piperidine $C_{3,5}$-H), 1.48 (m, 2H, piperidine C_4-H); ^{13}C-NMR (300 Hz, DCM); 166.9 (*C*OO-CH_3), 163.1 (phenyl C_4), 131.7 (phenyl C_2 and C_6), 123 (phenyl C_1), 114.5 (phenyl C_3 and C_5), 66.6 (NCH_2CH_2O), 55.4 (piperidine C_2 and C_6), 54.3 (NCH_2CH_2O), 52 (CH_3), 26.4 (piperidine C_3 and C_5), 24.6 (piperidine C_4); MS (EI, 70ev) *m/z* (%): 264 (M+1, 9.98), 247 (4.32), 237 (2.83), 217 (3.67), 207 (3.62), 135 (19.16), 112 (44.02), 104 (45.26), 97 (100), 76 (12.01). GC-MS (EI), rt=36.543 min, m/z (%): 249.8 [M+1]. Anal. Calcd. for $C_{15}H_{21}NO_3$ (263.34): C, 68.42; H, 8.04; N, 5.32; Found: C, 68.09; H, 8.36; N, 4.97.

Methyl 4-[2-(1-morpholinyl)ethoxy]benzoate ester (9c): Yield 62%; ^{1}H-NMR (300 Hz, DCM); δ 8 (d, 2H, J=9 Hz, phenyl $C_{2,6}$-H), 6.97 (d, 2H, J=9 Hz, phenyl $C_{3,5}$-H), 4.17 (t, 2H, NCH_2CH_2O), 3.88 (s, 3H, CH_3), 3.7 (t, 4H, morpholine $C_{2,6}$-H), 2.81 (t, 2H, NCH_2CH_2O), 2.56 (t, 4H, morpholine $C_{3,5}$-H); ^{13}C-NMR (300 Hz, DCM); 166.9 (*C*OO-CH_3), 162.9 (phenyl C_4), 131.8 (phenyl C_2 and C_6), 123.1 (phenyl C_1), 114.5 (phenyl C_3 and C_5), 67.2 (morpholine C_2 and C_6), 66.3 (NCH_2CH_2O), 57.8 (NCH_2CH_2O), 54.5 (morpholine C_3 and C_5), 52 (CH_3); MS (EI, 70ev) *m/z* (%): 266 (M+1, 16.53), 248 (0.79), 234 (0.94), 221 (0.87), 154 (0.76), 147 (4.72), 134 (7.23), 114 (30.28), 100 (59.48), 92 (10.23), 70 (44.07). GC-MS (EI), rt=36.412 min, m/z (%): 252 [M+1]. Anal. Calcd. for $C_{14}H_{19}NO_4$ (265.31): C, 63.38; H, 7.22; N, 5.28; Found: C, 63.32; H, 7.46; N, 5.39.

Results and Discussion

Chemistry

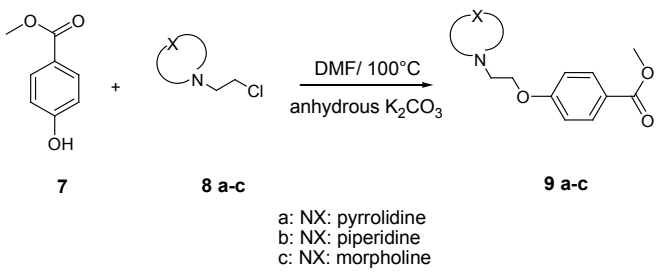
The aimed methyl 4-[2-(cyclized amino)ethoxy]benzoate esters 9a-c were synthesized by alkylation of methyl p-hydroxybenzoate 7 with appropriate 2-chloroethylamines 8a-c in DMF using K_2CO_3 in good yields (Scheme 1), following a reported method [18]. In the present work, basic cyclic amine esters were selected to include different functionalities of classical 5 to 6-membered rings namely pyrrolidine and piperidine as mono-heteroatom cycles and morpholine as di-heteroatom cycle. Structures of newly synthesized purified esters were confirmed by ^{1}H-NMR, ^{13}C-NMR, mass spectral analysis (MS) and gas chromatography-mass spectrometry (GS-MS).

Spectral analysis

^{1}H-NMR spectral analysis: ^{1}H-NMR spectra of synthesized compounds 9a-c, recorded using dichloromethane as solvent, exhibited two doublet signals for aromatic protons between 6.95 and 8 ppm. Ethoxy protons showed triplet signals between 2.77 and 4.17 ppm along with a singlet of methyl protons at 3.88 ppm. These signals were common in the three spectra where they correspond to common parts of structures. A singlet at 5.4 is common in all spectra referring to solvent proton. The heterocycle protons exerted signals ranging between 1.48 and 2.63 ppm according to deshielding exerted by nitrogen and oxygen in ring structures.

^{13}C-NMR spectral analysis: ^{13}C-NMR spectra and DEPT-135 revealed distinguished aromatic carbons absorption peaks between 110-150 ppm. Phenolic ether and carboxyester carbons displayed signals at higher values in the deshielded region 166.9 and 163 ppm, respectively. Ethoxy and methyl carbons signals resonated between 52 and 67 ppm. The cyclic amines which are the different part among structures, showed carbon signals over wide range of shifts due to difference in distribution of oxygen and nitrogen. This can be clearly revealed by difference in carbon shifts around heterocyclic atoms. Neighboring carbons appeared to have signals between 54 and 56 ppm. Pyrrolidine $C_{3,4}$ and piperidine $C_{3,5}$ resonated at 23 and 26, respectively. However, the presence of oxygen in morpholine exerted de-shielding effect on carbons 2 and 6 shifting them to 67.2 ppm. C_4 of piperidine revealed a distinct signal at 24.6.

Mass spectral analysis: Mass spectra of benzoate ester derivatives 9a-c showed molecular ion peaks at m/z [M+1] values 250, 264 and 266 for 9a-c, respectively. These values are consistent with molecular mass values of synthesized analogs. Base peak, 100% relative abundant ion peak, together with other significant peaks gave an overview on general fragmentation pattern. The most abundant fragments in mass spectrum of compound 9a showed peaks at m/z 84 appropriate for 1-methylpyrrolidine ($C_5H_{10}N$) and at 121 as benzoate ion ($C_7H_4O_2$), with 100.00 and 14.77 relative intensities, respectively. Similarly for compound 9b spectrum, peaks appeared at m/z 97 and 104 corresponding to 1-methylpiperidine ($C_6H_{12}N$) and benzoyl group (C_7H_4O), respectively. The relative intensities of the mentioned fragments were 100.00 and 45.26, respectively. While for



Scheme 1: Synthesis of Methyl 4-[2-(cyclized amino)ethoxy]benzoate esters 9a-c.

9c, the mass spectrum revealed major peaks at m/z 100 appropriate for 4-methylmorpholine ($C_5H_{10}NO$) and at 114 corresponding to 4-ethylmorpholine ($C_6H_{12}NO$), with relative intensities 59.8 and 30.28, respectively.

GC-MS analysis: Gas chromatography- mass spectrometry was run under the following conditions: inlet temperature 220°C; carrier gas Helium; flow rate 1.5 ml/min. A 0.2 µl of sample, with 5000 ppm concentration, was injected into GC using split-injection mode with split-ratio 100:1. The temperature of GC oven was programmed as follows: 70°C for first 15 min then it increased to 180°C till 55 min. Retention time values of the three compounds were very close to each other, 35.543, 35.526 and 35.412 for 9a-c respectively. Molecular ion peaks at m/z [M+1] values shown by the mass spectrophotometer detector were 250 for both 9a and 9b, while it is recorded to be 252 for 9c compound. This result suggested the idea that compounds 9b and 9c, piperidinyl and morpholinyl derivatives underwent an ester hydrolysis and liberation of the methyl group. Controversially, pyrrolidinyl analog 9a didn't undergo an ester hydrolysis and liberation of the methyl group.

Conclusions

Supporting the continuous process of SERMs structural optimization and design of novel related analogs, besides the obligation to assist chemical society with unprecedented information, valuable synthetic ester intermediates were synthesized, first time purified and spectrally characterized. In this study, series of methyl 4-[2-(cyclized amino)ethoxy]benzoate esters including pyrrolidine, piperidine and morpholine groups were prepared and confirmed by ^{1}H-NMR, ^{13}C-NMR, MS and GS-MS methods. These intermediates and their corresponding acids are not only useful to import the antagonistic basic tail during SERMs synthesis, but also authors believe that they could be successfully used as carbon source in ring closure step that simultaneously incorporates vital antagonistic tail in future studies.

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Conflicts of Interest

The authors declare no conflict of interest.

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