Ultrasound-assisted synthesis of benzothiazepines and assessment of their in vitro
acetylcholinesterase inhibition activity

Azhar U. Khan\textsuperscript{a}, Nazia Malik\textsuperscript{a}, Mahboob Alam\textsuperscript{b} and Dong-Ung Lee\textsuperscript{b*}

\textsuperscript{a}Department of Chemistry, Aligarh Muslim University, Aligarh, India; \textsuperscript{b}Division of Bioscience, Dongguk University, Gyeongju, Republic of Korea

(Received 12 November 2013; final version received 26 March 2014)

A series of steroidal 1,5-benzothiazepine and its derivatives have been synthesized by the reaction of \(\alpha,\beta\)-unsaturated ketones with 2-aminothiophenol using small amount of dimethylformamide (DMF) as a solvent and catalytic amount of acetic acid at 45–50\(^\circ\)C under ultrasonic irradiation. This method provides several advantages such as the shortest reaction time, high yields, simple work-up procedure, and purification of products by nonchromatographic methods. All the synthesized compounds were screened for their acetylcholinesterase (AChE) inhibition activity. These compounds exhibited moderate AChE inhibition activity as compared to the standard drug, tacrine. Compound 5 showed the highest inhibition among all benzothiazepines. The AChE inhibition activity of the compound 5 was further investigated with the help of \textit{in silico} docking study to predict the active sites.

\textbf{Keywords}: ultrasound irradiation; unsaturated ketones; aminothiophenol; benzothiazepines; acetylcholinesterase

1. Introduction

The neurodegenerative disorder of the central nervous system is characterized by loss of cognitive ability and severe behavior abnormalities, resulting in the degradation of intellectual and mental activities. These symptoms are linked to a deficiency in the brain neurotransmitter acetylcholine and recognized as Alzheimer’s disease (AD) (1–5). According to the World Health Organisation (WHO), AD is one of the fastest growing health hazards because of its unknown etiology and irreversible progressive nature which ultimately results in the loss of thinking abilities (6, 7). Several efforts have been made in order to minimize the negative effects of the AD and carry out its preliminary diagnosis and therapeutic control. One of the emerging and reliable strategies is the enhancement of cholinergic neurotransmission which has been considered as one potential therapeutic approach against AD. One treatment approach is to enhance cholinergic function by the use of acetylcholinesterase (AChE) inhibitors to increase the amount of acetylcholine present in the synapses between cholinergic neurons (8–12). AChE inhibitors like tacrine, one of the most extensively studied AChE inhibitors, have been shown to significantly improve cognitive function in AD.

Benzo-annelated compounds of thiazepines commonly known as benzothiazepines occupy a unique place in medicinal and biological chemistry due to their wide spectrum of pharmacological properties (13–20). In spite of the immense biological activities of seven-membered ring analogous benzothiazepine and synthetic importance, only a few methods for the preparation of 1,5-benzothiazepines are reported in literature (21–23). In recent years, extensive studies have been devoted to the synthesis of heterocyclic compounds by nonconventional conditions such as microwave- and ultrasound-assisted organic synthesis which are proved to be advantageous because of their shorter reaction times, very little or almost no use of solvents, and convenient work-up procedures. Hence, these routes are becoming more popular for organic chemists and have recently been reviewed (24–30). The term “ultrasound” generally refers to sound waves with frequencies greater than the upper limit of the human hearing range (\(\mu > 18\) kHz) and can remarkable effect on many physical and chemical processes. They are produced by a transducer which propagated by a series of compression and rarefaction cycles through solvent medium, and it causes the molecules to alter vibrational and rotational molecular states. During these states, the average distance between the molecules increases and decreases, respectively. Under appropriate conditions, the attractive forces of the molecules of the liquid may be overcome, causing the formation of bubbles in the rarefaction cycles. In case, the internal forces are high...
enough to ensure the collapse of these bubbles, very high local temperature (5000°C) and pressure (over 1000 bar) may be attained leading to the initiation of chemical reactions. This process by which the bubbles form, grow, and undergo violent collapse is known as cavitation (Figure 1).

Moreover, the presence of external factors such as reaction temperature and type of solvents also influences the cavitation phenomena followed by sonochemical reactions. The cavitation threshold increases with decrease in temperature of bulk solution. With increase in temperature ≥60°C, the solvent reaches its boiling point and produces larger number of cavitation bubbles concurrently acting as a barrier to sound transmission and nullifying the effectivity of ultrasound energy. In addition to temperature, the types of solvent directly affect the progress of reactions. Thus the solvent must be as inert, stable, and have high boiling point. However, diethyl ether is an exception. The beneficial effect of the sound energy/sound waves generated during cavitational collapse in ultrasound process has been utilized to accelerate a number of synthetically useful reactions during the last decade (31–35). There are various chemical transformations which can be activated by the use of ultrasound irradiation techniques and are well documented in the literature such as Reformatsky reaction (36), Ullmann condensation (37), Suzuki cross-coupling (38), oxidation of hydroquinones (39), and conversion of nitro compounds (40), etc. Ultrasound has also been employed for specific chemical applications where the conventional protocol needs drastic conditions or prolonged reaction times (41).

There are handful reports for the conventional synthesis of benzothiazepines employing rigorous reaction conditions like refluxing, use of mineral acid, anhydrous conditions, etc., but to the best of our knowledge, there is no report on the ultrasound-induced synthesis of steroidal benzothiazepines and their AChE inhibition activity. Although a few papers have appeared recently using this technique for steroidal transformation (42–45). Herein, we describe the use of ultrasound irradiation for the preparation of steroidal benzothiazepines using small amount of dimethylformamide (DMF) as a solvent containing catalytic quantity of acetic acid and their AChE inhibition activity. However, the present paper reports an environmentally benign protocol with higher yield. A comparative study has already been summarized in Supplemental material, Table S2. The role of DMF (46) can be explained as an energy transfer agent and homogenizer to increase the reaction

![Figure 1. Graphical representation of the sonochemical reaction setup and acoustic cavitation: (a) ultrasound range, (b) pressure wave cycle exceeds the attractive forces of the molecules, (c) sound transmission through a medium, and (d) sound propagation in a liquid showing cavitation bubble formation and collapse.](image-url)
temperature and is responsible for enhancement of yields while acetic acid act as a catalyst and can push the reaction toward the formation of the product. Furthermore, in silico molecular docking technique plays a key role in the drug design and discovery to predict the orientation of the docked molecule(s) at the active site, so the in silico studies of the synthesized compounds were also carried out to predict the active site of acetylcholine binding protein (AChBP; 2BYN.pdb) and the results obtained are presented.

The results are found to be encouraging and the ultrasonic procedure was found to be convenient, ecofriendly, and efficient method for the synthesis of benzothiazepines. These benzothiazepines were further screened for their plausible biological activities with respect to standard drugs.

2. Results and discussion

The synthesis of 5 α-cholestan[5,7-bc]-2’,3’-dihydro-1’,5’-benzothiazepine was carried out in a variety of solvents under ultrasonic irradiation in order to locate the best solvent and most favorable temperature range. Under these optimization conditions, DMF was found to be the most suitable one in terms of product yield and reaction time. The temperature range 45–50°C was found to be most viable as the temperature above this range produces larger number of cavitation bubbles concurrently acting as a barrier to sound transmission and nullifying the affectivity of ultrasound energy subsequently decreasing the overall yield of the product. Furthermore, with increase in temperature the reaction mixture starts behaving in a conventional manner thus restricting the overall yield and claiming longer reaction time. However, the addition of catalytic amount of acetic acid decreases the reaction time up to 10% of the total time. The addition of acetic acid may induce an electromeric effect thereby activating the carbonyl group which decreases the threshold energy of the reactants. A similar effect can be proposed for compounds 5 and 6. The optimization conditions are summarized in Table 1.

2.1. Chemistry

In continuation with our interest in the preparation of steroidal benzothiazepines, we carried out the reaction of easily accessible steroidal α,β-unsaturated ketones such as cholest-5-en-7-one (1) (47), 3 β-acetoxycholest-5-en-7-one (2) (48), and its analogs 3 β-chloro cholest-5-en-7-one (3) (49) and cholesta-3,5-diene-7-one (7) (48) with 2-aminothiophenol in the presence of catalytic amount of acetic acid in DMF under ultrasonic irradiation which afforded the corresponding steroidal [5,7-bc]-2’,3’-dihydro-1’,5’-benzothiazepines (4–6 and 8; Scheme 1), in fair yields (Supplemental material, Tables S1 and S2). The benzothiazepines (4–6 and 8) are identified on the basis of physical, microanalytical (Supplemental material, Table S1), spectral (IR, 1H NMR, and mass spectrometry [MS]) data, and comparison with authentic sample is given in the SI (50–52). This procedure provides a much more efficient and practical synthesis of the title compounds with the following advantages: significant shortening of the reaction time, higher yield, and ecofriendly as compared to the conventional methods. This is the first report on a rapid synthesis of the steroidal benzothiazepines where ultrasonic techniques have been used. The elemental analysis for compound 4 was found consistent with theoretical values for the corresponding compound and was found within ±0.4% of the theoretical values. Compound 4 gave diagnostic absorption IR bands at 3000 and 1600 cm⁻¹ (aromatic), 1582 cm⁻¹ (C = N), and 730 cm⁻¹ (C–S). Their stretching frequencies confirmed the condensation of 2-aminothiophenol with 1, leading the formation of 4.

| Solvent  | Temperature (°C) | Timea (min) | Isolated yield (%) |
|----------|-----------------|-------------|--------------------|
| MeOH     | RT 45–50        | 60–65       | 20 25 15           |
| EtOH     | RT 45–50        | 60–65       | 20 25 15           |
| CH₃CN    | RT 45–50        | 60–65       | 25 30 20           |
| CHCl₃    | RT 45–50        | 60–65       | 25 35 15           |
| 1,4-Dioxane | RT 45–50        | (75–85)    | 30 40 20           |
| THF      | RT 45–50        | 60–65       | 30 42 20           |
| DMF      | RT 45–50        | 60–65       | 35 60 20           |

*aAddition of catalytic amount of acetic acid.

The 1H NMR spectrum of 4 exhibited (50–52) two multiplets at δ 7.25 and 7.06 each integrating for two protons, assigned to aromatic protons. The 3(H) protons resonated as multiplets at δ 2.6 corresponding to C₆-H₂ and C₇-H. However, the angular (C₁₅-H₃), (C₁₃-H₃), and side chain methyls (C₂₁-H₃) and (C₂₅-H₃)₂ were observed at δ 1.2, 0.90, 0.83, and 0.70, respectively. In the 13C NMR spectrum of compound 4, the signals appearing between δ 113.1 and 143.1 ppm attributed to aromatic carbons while the carbon of C = N appeared at δ 167.5 ppm clearly indicated the formation of C = N which also supports the formation of compound 4. The spectral studies are in agreement with the possible structures (4 and 4a), but the proposed mechanism (50–52), IR bands, and the absence of NH grouping signal in the 1H NMR
favor the formation of 4. Hence the compound 4 has been identified as 5α-cholestan[5,7-bc]-2′,3′-dihydro-1′,5′-benzothiazepine (4) which was further supported by m.p., mixed m.p. (lit. m.p. 115 °C) (50–52), superimposed IR, and co thin layer chromatography (TLC) with authentic sample prepared according to literature methods. It is well documented that the formation of 1,5-benzothiazepines occurs by the reaction of α,β-unsaturated ketones and 2-aminothiophenol under acid-catalyzed conditions. It is a simple two-step process. The first step is the Michael addition of the mercapto group (−SH) to the β-carbon atom of the unsaturated ketone while the second step involves the ring closure of the Michael adduct to form the seven-membered heterocyclic ring with the elimination of water molecule (Scheme 2). Products (5 and 6) were also characterized on the basis of similar accounts and ruled out the formation of alternative possible structures 5a and 6a. Moreover, the mass spectrum of representative compound (4) further establishes its formation (see Supplemental material, Figure S1).

Under similar conditions, the dienone (7) on treatment with 2-aminothiophenol followed by column chromatography over silica gel afforded the adduct product (8), as an oil. The structure of oil (8) was established on the basis of similar accounts as described earlier, products (4–6). The formation of 8 was assumed to proceed through the Michael addition of sulfur in o-aminophenol on the δ-carbon double bond followed by intramolecular cyclization of −NH₂ on β-carbon atom of the unsaturated ketone (Scheme 2). All the spectral and analytical data for 4, 5, 6, and 8 are identical to those previously reported given in references [50–52] and supplemental material. 13C NMR spectral data of titled compounds are reported for first time. Table S2 gives a comparison of this method with that of conventional thermal method clearly illustrating the advantages in the microwave-assisted synthesis of benzothiazepines (4–6 and 8).

2.2. AChE inhibitory activity

The anti-cholinesterase effects of the compounds (4–6 and 8) were determined by modified Ellman’s spectrophotometric method using AChE from Electrophorus electricus with tacrine as reference compound. All the compounds were carefully measured and the results are shown in Table 1. The results were collected from at least three independent measurements. From the results obtained, compound 5 (IC₅₀ = 0.31 ± 0.1) exhibited significant inhibition on AChE among all these compounds. The improved activity of the compound 5 in comparison to compounds 4 (IC₅₀ = 0.78 ± 0.3), 6 (IC₅₀ = 0.45 ± 0.1), and 8 (IC₅₀ = 0.58 ± 0.03) can be explained on the basis of its skeleton and electronic properties at position 3 of the cholestane ring, and the presence of acetoxy group at C-3 of cholestane skeleton increases activity due to the formation of additional nonclassical bonds with amino acid residues of the protein and easily performs
as guest relation with receptor protein (host). The synthesized compounds were found to be fairly active with respect to the reference drug, tacrine.

2.3. Molecular docking

The AChE-inhibiting activity data of the active compound 5 were further investigated on structural basis by molecular modeling and docking study of AChBP (2BYN.pdb) using MVD and Discovery Studio 3.5 Client software to predict the affinity and orientation (Figure 1a and b) of the active site. The different bonds, i.e., hydrogen bonds, van der Wall forces, and hydrophobic behavior formed with amino acids were in good agreement with the predicted binding affinities obtained by molecular docking studies as verified by AChE-inhibiting activity where compound 5 (Figure 2a) was found to be the most active compound against AChBP compared with the standard drug which shows similar behavior in terms of docking studies. The activity of compound 5 can also be explained on structural basis (Figure 2b). The nonclassical bonds of the compound 5 were formed by amino acid residues surrounding the active gorge of AChE (AChBP) along with some water molecules of AChE protein. The N and S groups of the benzothiazepine could interact with THR36:N, THR36:OG1, GLU56:N, GLN57:N, and GLN57:N (attached with different atom of the same compound) at the AChBP of AChE through the hydrogen bond. Moreover, the presence of acetoxy group at position 3 of steroidal ring may enhance the activity of compound 5 forming some additional nonclassical bonds (Figure 2b) with amino acids residue of protein which revealed that derivative 5 of benzothiazepines could have better pharmacological activity among other derivatives 4, 6, and 8.

3. Experimental

All reagents were purchased from commercial sources and used without further purification. Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. Steroidal ketones were prepared according to the reported procedure. Sonication was performed in Branson-5210 ultrasonic cleaner with a frequency of 25 kHz and a nominal power of 250 W. Products were characterized by comparing physical
data with authentic samples and spectroscopic data. The IR spectra were recorded on Nujol/KBr pellets with a Pye Unicam SP3-100 spectrophotometer and its values are given in cm$^{-1}$. $^1$H NMR and $^{13}$C NMR spectra were measured on a Bruker AVANCE spectrometer at 400 and 125 MHz, respectively, in CDCl$_3$, and chemical shifts were recorded in $\delta$ ppm relative to the internal reference tetramethylsilane (TMS). Mass spectra were measured on a JMSD300 AIE MS-9 spectrometer using direct insertion technique at a source temperature of 250°C. The elemental analyses (% C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. TLC plates were coated with silica gel G and exposed to iodine vapors to check the purity as well as the progress of reaction.

3.1. Preparation of steroidal benzothiazepines 5–8: general procedure

The ketones (1, 2, 3, or 4; 1.13 mmol) and 2-aminothiophenol (4.76 mmol) were taken in DMF (5 mL) and glacial acetic acid (catalytic amount) was added. The reaction mixture was irradiation in the water bath of the ultrasonic cleaner at 45–50°C for 75–85 min. The reaction mixture was allowed to attain room temperature and treated with cold water. The solid separated was filtered, washed with water, and air dried. Recrystallization from ethanol afforded 5, 6, or 7, respectively, as solid, while in the case of 4 the usual work-up afforded 8 as an oily compound which was further purified by silica gel column chromatography. Comparative yields, melting points, elemental analysis, and spectral analysis (IR, $^1$H NMR, and MS) of the products are included in the SI. To the best of our knowledge, we are reporting $^{13}$C NMR analysis of the known compounds here for the first time and are given in the following.

3.2. Spectral data for the synthesized compounds

3.2.1. 5$\alpha$-Cholestan[5,7-bc]-2',3'-dihydro-1',5'-benzothiazepine (4)

M.p. 115 °C [Lit. (52)]; IR, $^1$H NMR, and MS are in accordance with previously reported data and are included in the SI; $^{13}$C NMR (CDCl$_3$) ($\delta$, ppm) 34.4 (C-1), 22.5 (C-2), 24.9 (C-3), 40.5 (C-4), 46.1 (C-5), 31.3 (C-6), 167.5 (C-7), 46.3 (C-8), 48.3 (C-9), 37.9 (C-10), 22.4 (C-11), 39.3 (C-12), 43.1 (C-13), 56.3 (C-14), 26.2 (C-15), 28.6 (C-16), 55.9 (C-17), 12.5 (C-18), 22.2 (C-19), 35.9 (C-20), 18.7 (C-21), 36.3 (C-22), 24.6 (C-23), 30.5 (C-24), 27.8 (C-25), 22.6 (C-26/C-27), 134.3, 143.1, 117.0, 128.2, 122.8, and 133.1 (aromatic carbons).

3.2.2. 5$\alpha$-Cholestan[5,7-bc]-2,3-dihydro-1',5'-benzothiazepin-3-yl acetate (5)

M.p. 148 °C [Lit. (52)]; IR, $^1$H NMR, and MS are in accordance with previously reported data and are included in the SI; $^{13}$C NMR (CDCl$_3$) ($\delta$, ppm) 34.6 (C-1), 27.5 (C-2), 74.1 (C-3), 31.9 (C-4), 46.3 (C-5), 52.9 (C-6), 167.1 (C-7), 170.7 (CH$_3$COO−), 21.1 (CH$_3$COO−), 134.4, 139.9, 113.7, 128.1, 121.9, and 131.1 (aromatic Carbons) and for other signals are in close accord with the cholestane series.

3.2.3. 5$\alpha$-Cholestan[5α,7-bc]-2',3'-dihydro-1',5'-benzothiazepin-3β-yl chloride (6)

M.p. 225 °C [Lit. (52)]; IR, $^1$H NMR, and MS are in accordance with previously reported data and are included in the SI; $^{13}$C NMR (CDCl$_3$) ($\delta$, ppm)
34. 1 (C-1), 28.1 (C-2), 58.9 (C-3), 31.6 (C-4), 46.6 (C-5), 53.0 (C-6), 166.9 (C-7), 134.4, 139.9, 113.7, 128.1, 121.9, and 131.1 (aromatic carbons) and for other signals are in close accord with the cholestane series.

3.2.4. 5 α-Cholestan[3,5-bc]-2,3,4,5-tetrahydro-1′,5′-benzothiazepin-7-one (8) M.p. 225 °C [(Lit. (52)]; IR, 1H NMR, and MS are in accordance with previously reported data and are included in the SI; 13C NMR (CDCl3) (δ, ppm) 33.3 (C-1), 31.4 (C-2), 40.9 (C-3), 31.8 (C-4), 55.6 (C-5), 52.9 (C-6), 209.3 (C-7), 46.2 (C-8), 37.9 (C-9), 43.5 (C-10), 22.0 (C-11), 32.8 (C-12), 41.5 (C-13), 48.1 (C-14), 24.2 (C-15), 28.1 (C-16), 53.9 (C-17), 12.7 (C-18), 23.2 (C-19), 35.1 (C-20), 18.3 (C-21), 36.2 (C-22), 24.8 (C-23), 31.0 (C-24), 26.9 (C-25), 2 × 22.4 (C-26/C-27), 134.5, 144.2, 113.2, 127.7, 122.6, and 130.8 (aromatic carbons).

3.2.5. In vitro acetylcholine esterase inhibition activity The in vitro inhibition of AChE for the synthesized compounds was screened spectrophotometrically by modified Ellaman’s coupled enzyme assay method (53) using tacrine as reference. Electric eel AChE (Type-VI-S, EC 3.1.1.7) was used as the enzyme sources while acetylthiocholine iodide as substrates and 5,5′-dithio-bis(2-nitrobenzoic) acid (DTNB) was also used in the anti-cholinesterase activity determination. In this producer, the assay solution was composed of 0.1 mL of each sample (1 mg/mL in methanol), 0.02 mL of substrate (75 mM acetylthiocholine iodide in H2O), and 0.1 mL of Ellman reagent (10 mM DTNB and 17.85 mM sodium bicarbonate in sodium phosphate buffer solution, pH 7.0). The reaction mixture was incubated for 15 min at 25°C. An enzyme solution of 25 μL containing 0.28 U/mL (commercial AChE) was added to above mixture with 3.0 mL of sodium phosphate buffer and then further incubated for 5 min at 25°C. The resulting solutions were placed in a spectrophotometer. For nonenzymatic reaction, the assays were carried out with a blank containing all components except AChE. The difference of absorbance at 412 nm for sample and control was calculated as an inhibition rate (%). The percentage of enzyme inhibition was calculated using the following formula.

\[
\text{% inhibition} = \frac{E - S}{S} \times 100
\]

where E is the activity of the enzyme without test sample and S is the activity of enzyme with test sample. Tacrine was used as a standard inhibitor. The experiments were done in triplicate and the results were expressed as average values. AChE inhibitor activities of synthesized title compounds are presented in Table 2.

3.2.6. In silico studies The retrieved protein “AChBP” (2BYN.pdb; www.rcsb.org/pdb) was improved using import and preparation option of MVD software, and missing bond order, hybridization state, angle, and flexibility for achieving reliable potential binding site in receptor. All the compounds were designed and structure was analyzed using ChemDraw Ultra3D software and then these structures were energetically minimized using MM2 force field with RMS Gradient set to 0.0001, and coordinates of compounds were checked using program for generating molecular topologies (PRODRG). Ligands’ structural properties were achieved through LigandScout. Discovery Studio 3.5 Client (54), MVD (55), and LigandScout (56) were used to perform molecular docking and energy profile of ligand–receptor interaction, independently.

4. Conclusions Benzothiazepines of cholestane series were synthesized using ultrasound irradiation for the first time with high yields. A variety of solvents were employed in order to find the best solvent in terms of product yield and reaction time. The AChE inhibitory activities of the derivatives were evaluated in vitro and compound 5 was found to possess better AChE inhibition activity. The appreciable activity of compound 5 (IC50 = 0.31 ± 0.1) was further verified hypothetically by using molecular docking study. It is inferred from docking study that compound 5 exhibits better AChE inhibitory activity because it is better H-bond acceptor and has proper orientation. Moreover,
compound 5 contains acetoxy group at position 3 of cholestane skeleton which enhances additional bond formation leading to better inhibitory activity.

Acknowledgments
We are grateful to the Chairman, Department of Chemistry, AMU, Aligarh, for providing necessary facilities.

Supplemental material
All Supplemental material is available alongside this article on www.tandfonline.com – go to http://dx.doi.org/10.1080/17518253.2014.909889

References
(1) Rosenberry, T.L. Adv. Enzymol. Relat. Areas Mol. Biol. 1975, 43, 103.
(2) Perry, E.K.; Tomilinson, B.E.; Blessed, F.; Bergmann, K.; Gibson, P.H.; Perry, R.H. Br. Med. J. 1978, 6150, 1457.
(3) Terry, A.V., Jr.; Buccafusco, J.J. Pharmacol. Exp. Ther. 2003, 306, 821.
(4) Selkoe, D.J. Physiol. Rev. 2001, 81, 741.
(5) Katzman, R.; Saitoh T. FASEB J. 1991, 5, 278.
(6) Terry, A.V.; Callahan, P.M.; Hall, B.; Webster, S.J. Pharmacol. Biochem. Behav. 2011, 99, 190.
(7) Mankil, J.; Moonsoo, P. Drug Dev. Res. 2002, 57, 118.
(8) Becker, R.E. Therapy of the Cognitive Deficit in Alzheimer’s Disease: The Cholinergic System. In Cholinergic Basis of Alzheimer’s Therapy: Becker, R.E., Giacobini, E., Eds.; Berkhauser: Boston, 1991, pp. 1–22.
(9) Parnetti, L.; Senin, U.; Mecocci, P. Drugs 1997, 53, 752.
(10) Brinton, R.D.; Yamazaki, R.S. Pharmaceut. Res. 1998, 15, 386.
(11) Hardy, J.; Selkoe, D.J. Science 2002, 297, 353.
(12) Tolnay, M.; Probst, A. Neuropathol. Appl. Neurobiol. 1999, 25, 171.
(13) Sarro, G.D.; Chimirri, A.; Sarro, A.D.; Gitto, R.; Zappala, M. Eur. J. Med. Chem. 1995, 30, 925.
(14) Ambrogi, V.; Furlani, A.; Grandolini, G.; Papaoannou, A.; Perioli, L.; Scarcia, V.; Tuttobello, L. Eur. J. Med. Chem. 1993, 28, 659.
(15) Grandolini, G.; Perioli, L.; Ambrogi, V. Eur. J. Med. Chem. 1994, 34, 701.
(16) Mane, R.A.; Ingh, D.B. Ind. J. Chem. 1982, 21B, 973.
(17) Jadhar, K.P.; Ingh, D.B. Ind. J. Chem. 1983, 22B, 180.
(18) Reddy, R.J.; Ashok, D.; Sharma, P.N. Ind. J. Chem. 1993, 32B, 404.
(19) Shetgiri, N.P.; Nayak, B.K. Ind. J. Chem. 2003, 42B, 683.
(20) Tollefson, M.B.; Kolodziej, S.A.; Fletcher, T.P.; Vernier, F.W.; Beaudry, J.A.; Keller, B.T.; Reitz, B.D. Bioorg. Med. Chem. Lett. 2003, 13, 3727.
(21) Leng, C.L.; Lam, Y.; Lee, S.Y. Tetrahedron Lett. 2001, 42, 109.
(22) Prakash, O.; Kumar, A.; Sadana, A.; Prakash, R.; Singh, P.S.; Chramunt, R.M.; Sanz, D.; Alkorta, I.; Elguero, J. Tetrahedron 2005, 61, 6642.
(23) Kodomari, M.; Noguchi, T.; Aoyama, T. Synth. Commun. 2004, 34, 1483.
(24) Abd El-Rahman, N.M.; Saleh, T.S.; Mady, M.F. Ultrasound. Sonochem. 2009, 16, 74.
(25) Breitner, M.C.; Wilkens, E.; Ritter, M.; Siqueira, G. M.; Cunico, W.; Pereira, C.M.P.; Freitag, R.A. Ultrasound. Sonochem. 2011, 18, 704.
(26) Siqueira, G.M. Ultrasound. Sonochem. 2010, 17, 281.
(27) Mason, T.J.; Peters, D. Practical Sonochemistry, 2nd ed.; Ellis Horwood: London, 2002.
(28) Luche, J.L. Synthetic Organic Sonochemistry; Plenum Press: New York, 1998.
(29) Li, J.T.; Yang, W.Z.; Wang, S.X.; Li, S.H.; Li, T.S. Ultrasound. Sonochem. 2002, 9, 237.
(30) Stefani, H.A.; Pereira, C.M.P.; Almeida, R.B.; Braga, R.C.; Guzen, K.P.; Cella, R. Tetrahedron Lett. 2005, 46, 6833.
(31) Mason, T.J.; Lorimer, J.P. Sonochemistry: Theory, Application and Uses of Ultrasound in Chemistry; John Wiley and Son: New York, 1988.
(32) Cravotto, G.; Cintas, P. Chem. Soc. Rev. 2006, 35, 180.
(33) Suslick, K.S. Ultrasound, Its Chemical, Physical and Biological Effects; VCH: Weinheim, 1988.
(34) Manson, T.J. Chem. Soc. Rev. 1997, 26, 447.
(35) Brinton, R.D.; Yamazaki, R.S. Ultrasound. Sonochem. 1994, 1, S119.
(36) Ross, N.A.; Bartsch, R.A. J. Heterocycl. Chem. 2001, 39, 1255.
(37) Robin, M.; Pique, V.; Faure, R.; Glay, J. J. Heterocycl. Chem. 2002, 39, 1083.
(38) Rajagopal, R.; Jariakote, D.V.; Srinivasan, K.V. Chem. Commun. 2002, 61, 616.
(39) Singh, V.; Sapehiyia, V.; Kad, G.L. Synthesis 2003, 2, 198.
(40) Chandrashekar, S.; Narimulu, C.H.; Jagadeshwar, V. Synlett. 2002, 5, 771–773.
(41) Li, J.T.; Bian, Y.J.; Zang, H.J.; Li, T.S. Synth. Commun. 2002, 32, 547.
(42) Dayal, B.; Ertel, N.H. Lipids 1998, 33, 333.
(43) Marwah, P.; Marwah, A.; Ladry, H.A. Tetrahedron 2009, 59, 2273.
(44) Skoda, F.R.; Peter, P.; Horvath, I.; Tuba, Z.; Kollar, L. Steroids 2002, 67, 709.
(45) Kurup, P.S.; Wahala, K. Steroids 2006, 71, 54.
(46) Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. Tetrahedron Lett. 1986, 27, 4945.
(47) Anagnostopoulos, E.; Fieser, L.F. J. Am. Chem. Soc. 1954, 76, 532.
(48) Baker, R.H.; Squire, E.N.; J. Am. Chem. Soc. 1980, 102, 1487.
(49) Milburn, A.H.; Truter, E.V. J. Chem. Soc. 1956, 1736.
(50) Mushfiq, M.; Iqbal, N. J. Chem. Res. (S). 1987, 274.
(51) Mushfiq, M.; Mudgal, G. J. Chem. Res. (S). 1992, 168.
(52) Mushfiq, M.; Iqbal. N. Ind. J. Chem. 1998, 27B, 173.
(53) Ellman, G.L.; Courtney, K.D.; Andres, V.; Featherstone, R.M. *Biochem. Pharmacol.* **1961**, *7*, 88.
(54) Accelrys Software Inc. *Discovery Studio Modeling Environment Release 3.1*; Accelrys Software Inc.: San Diego, 2011.
(55) Thomsen, R.; Christensen, M.H. *J. Med. Chem.* **2006**, *49*, 3315.
(56) Wolber, G.; Dornhofer, A.A.; Langer, T.J. *Comput. Aided Mol. Des.* **2006**, *20*, 773.