Asian Journal of Chemistry; Vol. 27, No. 11 (2015), 4092-4096

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.19102

Synthesis, Crystal Structure and Cholinesterase Enzymes Inhibitory Activities of New Pyridine Alkaloid Derivative

RAZA MURAD GHALIB[1,2,*], ROKIAH HASHIM[3], SAYED HASAN MEHDI[3], M. FÁTIMA C. GUEDES DA SILVA[4], OTHMAN SULAIMAN[3], FIONA HOW NI FOONG[2], FUMIO KAWAMURA[5], ALI JAWAD[6], YOUSIF ALGAMAL[1], KIT-LAM CHAN[7] and VIKNESWARAN MURUGAIYAH[8]

[1]Department of Chemistry, Faculty of Sciences and Arts–Khulais, University of Jeddah, Khulais, P.O. Box-355, Postal Code-21921, Kingdom of Saudi Arabia
[2]Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
[3]School of Industrial Technology, Universiti Sains Malaysia, Pulau-Pinang 11800, Malaysia
[4]Centro de Química Estrutural, Complexo I, Instituto Superior Técnico, Av. Rovisco Pais, 1049-00 Lisboa, Portugal
[5]Wood Extractives Laboratory, Department of Biomass Chemistry, Forestry and Forest Products Research Institute, Tsukuba 305-8687, Japan
[6]Department of Applied Physics, Zakir Husain College of Engineering and Technology, Aligarh Muslim University, Aligarh-202 002, India
[7]Discipline of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Pulau-Pinang 11800, Malaysia
[8]Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Pulau-Pinang 11800, Malaysia

*Corresponding author: Tel: +966 536961121; E-mail: raza2005communications@gmail.com

Received: 10 February 2015; *Accepted*: 31 March 2015; *Published online*: 16 July 2015; AJC-17410

A new pyridine alkaloid derivative named as 2-(6-benzyl-4-oxo-5-phenyl-1,4-dihydro pyridine-3-yl)-benzoic acid ethylester (**3**) has been prepared by the reaction of ninhydrin with 1,3-diphenylacetone *p*-tosylhydrazone and the structure has been established with the help of spectral analysis and X-ray analysis. The title compound demonstrated potent inhibitory activity against butyrylcholinesterase (BChE; IC_{50} = 4.91 μM) comparable to physostigmine (IC_{50} = 4.72 × 10^{-1} μM). However it showed moderate inhibitory activity against acetylcholinesterase (AChE; IC_{50} = 82.00 μM)). It was BChE selective over AChE, in contrast to physostigmine, which was more AChE selective. Being a potent and selective BChE inhibitor, it may serve as a new class of drug for prevention of the progression of neurodegeneration as well for symptomatic treatment of Alzheimer patient.

Keywords: Pyridine alkaloid, Acetylcholinesterase, Butyrylcholinesterase.

INTRODUCTION

The word alkaloids, was first introduced by the German chemist Carl Friedrich Wilhelm Meißner in 1819. Alkaloids are organic natural products those contain mostly basic nitrogen atoms. Except carbon, hydrogen and nitrogen, alkaloids may also have oxygen, sulfur, chlorine, bromine and phosphorus. Pyridine alkaloids contain nitrogen in heterocyclic saturated ring, *e.g.* nicotine in the *Nicotiana* species and atropine in A*tropa belladonna*. Twenty percent of plant species have alkaloids contents. The role of alkaloids in plant is not very clear. They are supposed to provide defense against herbivores and pathogens. Alkaloids are not only common in plants species but have also been found in frogs, ants, butterflies, bacteria, sponges, fungi, spiders, beetles and mammals *etc*. Some frogs produce poisonous alkaloids in the skin or secretory glands those works as a chemical defense against predation. Many synthetic compounds of same structures also known as alkaloids[1]. Synthetic pyridine alkaloid derivatives are biologically very active and versatile in the pharmaceutical industry. They are having antiviral, anticancer, antialzheimer, antichagasic, antioxidant, antibacterial, antidote, antidiabetic, antileishmanial, antitubercular, antithrombin, anticoagulant and antifungal activities[2]. In a study, Nadri *et al.*[3] reported new benzofuranone based derivatives of the pyridinium type; having potent AchE inhibitory activity in nanomolar concentration range. Furthermore, Attaby *et al.*[4] synthesized new pyridine compounds having remarkable antialzheimer activity. Alzheimer disease (AD) is a chronic and progressive neurodegenerative disease. The biochemical deficits of this disease are reduced levels of acetylcholine due to substantial reduction in the activity of choline acetyltransferase. According to the cholinergic hypothesis, there is an irreversible deficiency in cholinergic functions in brain that leads to memory impairment in Alzheimer patients[5]. Therefore, in order to sustain the level of remaining acetylcholine and enhance cholinergic transmission, cholinesterase enzymes inhibitors may be used as treatment modalities.

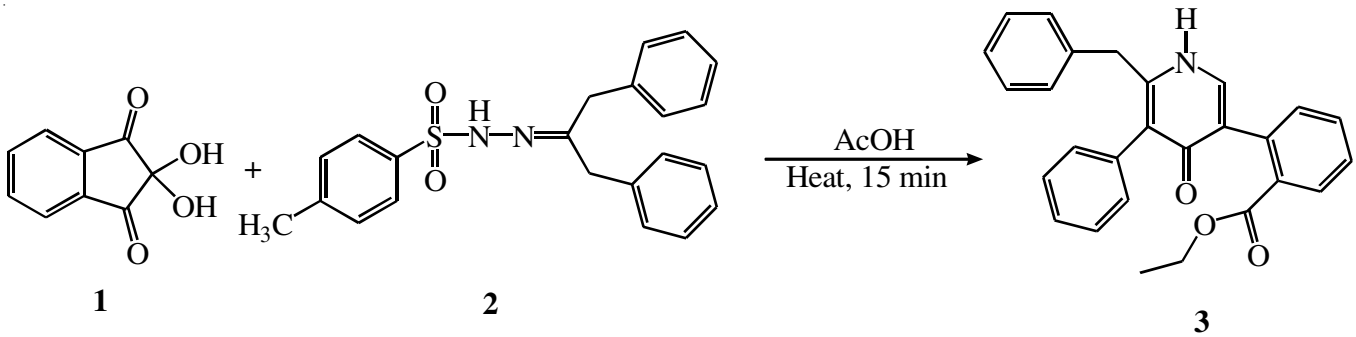
Tosylhydrazones have versatile uses in organic synthesis. 1,3-Diphenylacetone *p*-tosylhydrazone in THF solvent is applied usually as an indicator for the titration of alkyllithium reagents[6]. Tosylhydrazones of carbonyl compounds were found to be readily cleaved into the corresponding carbonyl compounds by treatment with potassium peroxymonosulfate-acetone system[7]. Tosylhydrazones with R_2X (R_2 = Me, Et, benzyl; X = iodo, Br) in a 2-phase system, in the presence of a phase-transfer catalyst undergo N-alkylation[8]. Tosyl hydrazones undergo C-alkylation through an *in situ* sequence under phase-transfer conditions[9]. N-tosylhydrazones coupled with *ortho* substituted aryl halides to synthesize 4-arylchromenes, thiochromenes and related heterocycles[10]. *p*-Tolylsulfonyl-hydrazones are decomposed to *p*-toluenesulfinate and either olefin or aryldiazomethanes by alkali or alkoxide[11]. Tosyl-hydrazones undergo oxidation to tosylazoalkenes in presence of phenyltrimethyl ammoniumperbromide followed by basic treatment effected *in situ*[12]. N,N-ditosylhydrazones can be converted into either 3-alkyl olefins or simple alkylated hydrocarbons by reaction with methyland *tert*-butyllithium[13]. Arylsulfonylhydrazines having various substituents groups undergo reduction and cleavage of N-N bond to give arysulfo-namide derivatives and amido compounds, with activated raney nickel[14]. In an important study García-Muñoz *et al*.[15] reported metal free reaction of carboxylic acids with tosylhydrazones in basic media to give rise the corresponding esters. Zhou, *et al*.[16] also reported a metal-free method for the synthesis of esters in good yields *via* reductive coupling of N-tosyl-hydrazones with carboxylic acids. The present work is also an example of N-N bond breaking of 1,3-diphenylacetone *p*-tosylhydrazone in acetic acid, as well as a new metal-free C=C bond forming reaction has been discovered.

EXPERIMENTAL

FTIR spectrum was measured by direct transmittance by means of the KBr pellet technique using a Nicolet Impact 400 FTIR. The ^{1}H NMR and ^{13}C NMR spectra were scanned on a Bruker Avance spectrometer (400 MHz for ^{1}H NMR, DEPT-135 and 100 MHz for ^{13}C NMR) in $CDCl_3$ using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass was recorded on JEOL GCmate instrument in ionization mode. Elemental analysis was performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. The melting point was taken on Thermo Fisher digital melting point apparatus of IA9000 series by open capillary method and is uncorrected. All the chemicals (Sigma-Aldrich) and solvents (Merck) were purchased commercially and used without further purification. TLCs were taken on silica gel plates (silica gel 60 F_{254} on aluminium foil, Merck). Acetylcholinesterase from electric eel, 5,5'-dithiobis(2-nitrobenzoic acid), acetylcholine iodide, butyrylcholinesterase from equine serum, S-butyrylthiocholine chloride and physostigmine were purchased from Sigma (St. Louis, USA). All solvents used were of analytical grade.

Synthesis of 2-(6-benzyl-4-oxo-5-phenyl-1,4-dihydro pyridine-3-yl)-benzoic acid ethylester (3): A mixture of ninhydrin (**1**) (1.78 g, 10 mmol) and 1,3-diphenylacetone *p*-tosylhydrazone (**2**) (3.78 g, 10 mmol) in acetic acid; in molar ratio 1:1 were heated on water bath for 15 min (**Scheme-I**). TLC monitored the progress of the reaction at regular interval of every 5 min. The reaction mixture was dried on rotary evaporator at low pressure and then crystallized with diethyl ether-petroleum ether (1:1 v/v) mixture to give the transparent crystals of the unexpected title compound (**3**): Yield: 55 %; m.p. 197.8 °C; R_f 0.733 (petroleum ether: acetone 1:1 v/v); Anal. calcd. for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found C, 79.0, H, 5.31, N, 3.15 %; IR (KBr, ν_{max}, cm^{-1}): 3428, 3235, 3029, 2980, 2846, 2768, 1946, 1722, 1606, 1529, 1495, 1337, 1285, 1245, 1172, 1127, 1019, 919, 788, 758, 702, 627, 571; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 10.76 (1H, brs, N-H), 6.96-7.92 (a set of signals, 15H, Ar-H), 4.10 (2H, q, J_1 = 7.2, J_2 = 7.2 Hz, CH_2), 3.80 (2H, s, CH_2), 1.08 (3H, t, J = 7.6 Hz, CH_3); ^{13}C-NMR and DEPT-135 (100 MHz, $CDCl_3$, δ/ppm): 169.0 (C, C=O), 167.2 (C, C=O), 157.5 (C), 149.1 (C), 134.9 (C), 134.5(C), 132.3 (C), 131.9 (C),131.7 (CH), 131.6 (CH), 130.3 (CH), 130.2 (2xCH), 129.4 (CH), 129.1 (2xCH), 129.0 (2xCH), 128.8 (CH), 128.4 (2xCH), 127.9 (CH), 127.7(C), 127.5 (CH), 61.0 (CH_2), 35.9 (CH_2), 13.9 (CH_3); MS (*m/z,* (relative abundance, %)): 411.1481 ([M+2]$^+$, 2.6); 410.2574 ([M+1]$^+$, 8.2); 409.1753 ([M]$^+$, 2.5).

Solution and refinement of the crystal structure: Reflection data were measured at 293 K with a Bruker APEX2 CCD diffractometer in θ/2θ scan mode using graphite monochromated molybdenum radiation (λ 0.7107 Å). SMART was used for collecting frame data, indexing reflection and determination of lattice parameters. SAINT[17] was used for integration of intensity of reflections and scaling. SADABS[18] was used for absorption correction and SHELXTL[19] for space group, structure determination and least square refinements on F^2. All hydrogen atoms were placed in calculated positions for the purpose of structure factor calculation. All non-hydrogen atoms were refined anisotropically[19]. The crystallographic parameters of crystal structure of the title compound are presented in Table-1.



1 **2** **3**

Scheme-I: Route for synthesis of compound **3**

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT DETAILS

Empirical formula	$C_{27}H_{23}NO_3$
Formula weight	409.46
Crystal dimension (mm)	0.15 × 0.21 × 0.47
Temperature (K)	100(2)
λ (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions (Å)	a = 9.0668(7), b = 19.1151(15), c = 12.6437(9)
Cell angle	α = 90.00, β = 104.573(2), γ = 90.00
Z	4
Calculated density (g cm^{-3})	1.282
Absorption coefficient (μ, mm^{-1})	0.083
F(000)	864
θ-range for data collection (°)	2.55, 25.35
Index ranges	-10:10; -21:23; -15:15
Number of reflections (total)	3859
No. reflections collected	17123
No. reflections unique/observed	3859/3415
R_{int}	0.0321
Data/restraints/parameters	3859/0/280
Goodness-of-fit on F^2	1.09
R indices	R1 = 0.0545, wR2 = 0.1792
R indices (all data)	R1 = 0.0599, wR2 = 0.1870
Largest peak and hole (e $Å^{-3}$)	0.857, -0.788

[a]$R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b]$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$

Cholinesterase enzymes inhibitory assay: Cholinesterase enzymes inhibitory potential of test samples was evaluated using Ellman's microplate assay following method described by Ahmed and Gilani[20]. Physostigmine was used as positive control. Test samples and physostigmine were prepared in methanol. The concentration of methanol in final reaction mixture was 10 %. At this concentration, methanol has no inhibitory effect on both acetylcholinesterase and butyrylcholinesterase enzymes. For acetylcholinesterase (AChE) inhibitory assay, 140 μL of 0.1 M sodium phosphate buffer (pH 8) was first added to a 96-wells microplate followed by 20 μL of test samples (**3** or physostigmine) and 20 μL of 0.09 units/mL acetylcholinesterase enzyme. After 15 min of incubation at 25 °C, 10 μL of 10 mM 5,52-dithiobis(2-nitrobenzoic acid) was added into each well followed by 10 μL of 14 mM acetylthiocholine iodide. At 30 min after the initiation of enzymatic reaction, absorbance of the coloured end-product was measured using BioTek PowerWave X 340 Microplate Spectrophotometer at 412 nm. For butyrylcholinesterase (BChE) inhibitory assay, the same procedures as described above were followed except for the use of enzyme and substrate, which were butyrylcholinesterase from equine serum and S-butyrylthiocholine chloride, respectively. Each test was conducted in triplicate. Absorbencies of the test samples were corrected by subtracting the absorbance of their respective blank. A set of six concentrations was used to estimate the 50 % inhibitory concentration (IC_{50}). Percentage inhibition was calculated using the following formula:

$$\text{Inhibition}\,(\%) = \frac{\text{Absorbance of control} - \text{Absorbance test compound}}{\text{Absorbance of control}} \times 100$$

RESULTS AND DISCUSSION

The synthetic route is outlined in **Scheme-I**. The title compound was obtained as transparent crystals. The molecular formula was deduced as $C_{27}H_{23}NO_3$ by analysis of ^{13}C and ^1H NMR data in conjugation with DEPT results and this was further confirmed by EI-MS *m/z* 410.2574 $[M+1]^+$ (8.2 %). The ^{13}C NMR spectrum displayed 27 carbons, which were assigned by DEPT experiments to the resonances of 1 CH_3, 2 CH_2, 15 CH and 9 Cs. The ^1H NMR spectrum displayed signals integrating for 23 protons. A broad singlet (δ 10.76 ppm) integrating for one proton and an IR peak at 3428 is due to N-H proton. A set of signals from δ 6.96 to δ 7.92 ppm integrating for 15 protons are due to aromatic rings protons. A downfield quartet at δ 4.10 (2H, CH_2) and a upfield triplet at δ 1.08 (3H, CH_3) is cleary shows the presence to ethoxy group which is also confirmed by IR peaks at 2980, 2846 cm^{-1}. A sharp singlet at δ 3.80 is due two benzylic protons of the compound. All the ^{13}C NMR signal and IR peaks satisfies the title structre.

Single crystal X-ray analysis: The title compound crystallized in monoclinic space group $P2_1/c$. The bond distances and angles are presented in Table-1. An Ortep view with atom numbering scheme and the most relevant hydrogen bond interaction is shown in Fig. 1 and a packing diagram is depicted in Fig. 2. The molecules are structured in chains running along the c axis connected *via* strong hydrogen bonds involving the dihydropyridil moieties of vicinal entities with the N-H acting as donor to the O atom as acceptor. The C1 > C6 and C13 > C18 phenyl rings are virtually planar and make dihedral angle of 22.15(11)º with each other, while the C19 > C24 benzoate ring make a dihedral angle of 53.77(9)º with the pyridyl plane. In addition, the pyridyl and the attached phenyl (C13 > C18)

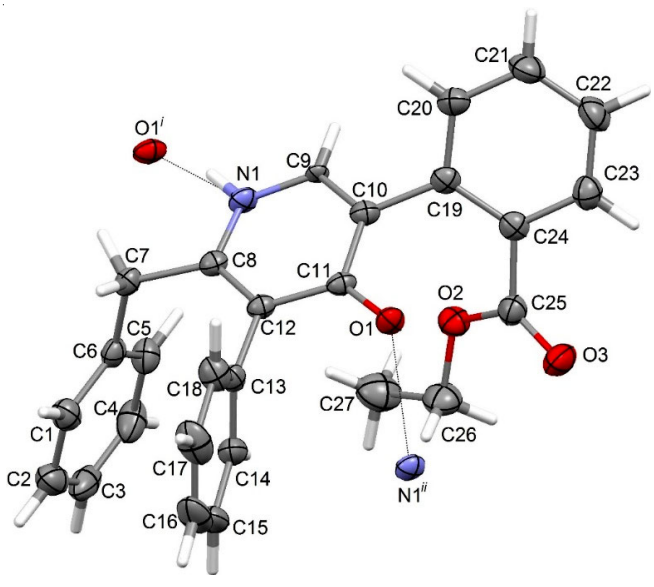


Fig. 1. ORTEP diagram of compound **3**, with atomic numbering scheme and showing the hydrogen bonding interactions. Ellipsoids are drawn at 50 % probability. Selected bond distances (Å) and angles (º): C8-N1 1.342(2), C9-N1 1.342(2), C11-O1 1.256(2), C8-C12 1.379(2), C9-C10 1.314(2), C10-C11 1.456(2), C11-C12 1.424(3), C24-C25 1.495(3), C25-O2 1.342(2), C25-O3 1.204(2), C26-O2 1.432(3); C9-N1-C8 125.01(15), C25-O2-C26 118.59(16). Hydrogen bond [*d*(H···A), ∠(DHA)]: N1-H1A···O1 1.87, 160.5º. Symmetry operations used to generate equivalent atoms: i) x,1/2-y,-1/2+z; ii) x,1/2-y,1/2+z

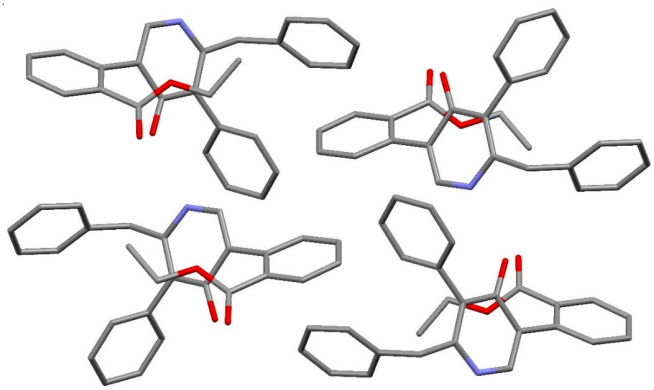


Fig. 2. Packing diagram of compound **3**, viewed down the crystallographic a axis

are almost perpendicular [acute angle of 81.12(10)º]. It is worth to mention the significant rotation of the carboxyl group from coplanarity with the aromatic ring to which it is attached [acute angle of 33.68(10)º] what may be attributed to the bulkiness of the adjacent residue. Moreover, the ethyl moiety is leaning towards the pyridyl ring what led to a considerable proximity between the H25C hydrogen and the plane of that group.

The packing diagram drawn to emphasize the structural features (Fig. 2) illustrates that the molecular packing is typical of monoclinic system with molecules lying in overturned orientations.

Enzyme inhibitory activities: Initial cholinesterase enzymes inhibitory activity of title molecule was evaluated at 100 µg/mL. At this concentration, compound had a potent enzyme inhibitory activity against both AChE and BChE with inhibition values of 92.13 and 105.92 %, respectively. Table-2 summarizes the IC_{50} and selectivity index of **3** and standard drug, physostigmine. The IC_{50} determination was carried out on both enzymes. At 100 µg/mL concentration, **3** has almost similar inhibitory activity on AChE and BChE. However, comparison of its IC_{50} values showed that **3** had more than sixteen times more potent inhibitory activity on BChE compared to AChE. On molar basis, **3** was approximately 594 times less potent than physostigmine against AChE. Interestingly, **3** was only approximately 10 times less potent than physostigmine on BChE. In addition, **3** was very selective towards BChE inhibition in contrast to physostigmine, which had more inhibitory effect on AChE. The most important changes observed in the brain of Alzheimer disease patients are the decrease of the neurotransmitter acetylcholine in hippocampus and cortex. Acetylcholinesterase (AChE) is the key enzyme involved in the metabolic hydrolysis of acetylcholine at cholinergic synapses in the central and peripheral nervous system. This observation led to the introduction of the acetylcholinesterase inhibitors to prolong the duration of action of acetylcholine and provide symptomatic treatment in Alzheimer disease[21]. In the present study, **3** showed moderate AChE inhibitory activity compared to physostigmine. Another enzyme, butyrylcholinesterase (BChE), expressed in selected areas of the central and peripheral nervous systems is also capable of hydrolysing acetylcholine, but its level may increase in Alzheimer disease[22,23]. In addition, BChE has an important role in the development and progression of Alzheimer disease where it is involved in formation and maturation of β-amyloid plaques[24-26]. It cleaves the amyloid precursor protein to β-amyloid that will progress to form β-amyloid plaques, which is responsible for the neurodegeneration. Thus, selective BChE inhibitor also prevents the formation of β-amyloid plaques[24]. Furthermore, according to Greig *et al.*[26] selective BChE inhibitor may be useful in ameliorating a cholinergic deficit in Alzheimer's disease due to increased BChE activity. Therefore, **3**, being a potent and selective BChE inhibitor may serve as a new class of drug for prevention of the progression of neurodegeneration as well for symptomatic treatment of Alzheimer patient.

Conclusion

A new molecule has been synthesized and crystallized. The structure was determined by using single crystal X-ray diffraction and spectral studies. Crystal structure depicted the formation molecular chains running along the *c* axis connected *via* strong hydrogen bonds. N-N bond breaking of 1,3-diphenylacetone *p*-tosylhydrazone occurred in acetic acid. The unexpected molecule resulted due to reaction with solvent during crystallization. The molecule demonstrated potent inhibitory activity against butyrylcholinesterase comparable to physostigmine. However, it showed moderate inhibitory activity against acetylcholinesterase. Compound **3** may serve as a new class of drug for prevention of the progression of neurodegeneration as well for symptomatic treatment of Alzheimer patient. It is an ester, thus, we can say that esters may have good effects on Alzheimer patients.

Supplementary material

CCDC 871660 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: þ44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

ACKNOWLEDGEMENTS

The authors would like to acknowledge USM and University of Jeddah for research facilities and thanks to Ms Lee Yuan E for her contribution in the present study.

TABLE-2
IC_{50} VALUES FOR INHIBITORY ACTIVITIES ON CHOLINESTERASE ENZYMES

Sample	AChE inhibition, IC_{50}		BChE inhibition, IC_{50}		Selectivity for	
	µg/mL	µM	µg/mL	µM	AChE[a]	BChE[b]
Compound **3**	33.55 ± 2.60	82.00	2.01 ± 0.36	4.91	0.06	16.70
Physostigmine	0.038 ± 0.007	1.38×10^{-1}	0.13 ± 0.02	4.72×10^{-1}	3.42	0.29

[a]Selectivity for AChE is defined as IC_{50}(BChE)/IC_{50}(AChE); [b]Selectivity for BChE is defined as IC_{50}(AChE)/IC_{50}(BChE)

REFERENCES

1. N.K. Gusarova, S.F. Malysheva, L.A. Oparina, N.A. Belogorlova, A.P. Tantsyrev, L.N. Parshina, B.G. Sukhov, R.T. Tlegenov and B.A. Trofimova, *ARKIVOC*, 260 (2009).
2. A. Chaubey and S.N. Pandeya, *Asian J. Pharm. Clin. Res.*, **4**, 5 (2011).
3. H. Nadri, M. Pirali-Hamedani, A. Moradi, A. Sakhteman, A. Vahidi, V. Sheibani, A. Asadipour, N. Hosseinzadeh, M. Abdollahi, A. Shafiee and A. Foroumadi, *DARU J. Pharm. Sci.*, **21**, 15 (2013).
4. F.A. Attaby, A.M. Abdel-Fattah, L.M. Shaif and M.M. Elsayed, *Afinidad*, **66**, 540 (2009).
5. V. Tougu, *Curr. Med. Chem-CNS Agents*, **1**, 155 (2001).
6. M.F. Lipton, C.M. Sorensen, A.C. Sadler and R.H. Shapiro, *J. Organomet. Chem.*, **186**, 155 (1980).
7. J.C. Jung, K.S. Kim and Y.H. Kim, *Synth. Commun.*, **22**, 1583 (1992).
8. S. Cacchi, F. La-Torre and D. Misiti, *Synthesis*, 301 (1977).
9. S. Cacchi, D. Misiti and M. Felici, *Synthesis*, 147 (1980).
10. E. Rasolofonjatovo, B. Tréguier, O. Provot, A. Hamze, E. Morvan, J.D. Brion and M. Alami, *Tetrahedron Lett.*, **52**, 1036 (2011).
11. W.R. Bamford and T.S. Stevens, *J. Chem. Soc.*, 4735 (1952).
12. G. Rosini and G. Baccolini, *J. Org. Chem.*, **39**, 826 (1974).
13. J.F.W. Keana, D.P. Dolata and J. Ollerenshaw, *J. Org. Chem.*, **68**, 3815 (1973).
14. T. Ueda and T. Tsuji, *NII-Electronic Library Service*, **9**, 71 (1961).
15. A.-H. García-Muñoz, M. Tomás-Gamasa, M.C. Pérez-Aguilar, E. Cuevas-Yañez and C. Valdés, *Eur. J. Org. Chem.*, **2012**, 3925 (2012).
16. A. Zhou, L. Wu, D. Li, Q. Chen, X. Zhang and W. Xia, *Chin. J. Chem.*, **30**, 1862 (2012).
17. SMART & SAINT Software Reference Manuals, version 4.0, Siemens Energy & Automation, Inc., Analytical Instrumentation, Madison, WI (1996).
18. G.M. Sheldrick, SADABS Software for Empirical Absorption Correction, University of Gottingen, Germany (1996).
19. SHELXTL, version 5.03, Siemens Energy & Automation, Inc., Analytical Instrumentation, Madison, WI (1996).
20. T. Ahmed and A.H. Gilani, *Pharmacol. Biochem. Behav.*, **91**, 554 (2009).
21. M. Weinstock and E. Groner, *Chem. Biol. Interact.*, **175**, 216 (2008).
22. M. Mesulam, A. Guillozet, P. Shaw and B. Quinn, *Neurobiol. Dis.*, **9**, 88 (2002).
23. A.N. Cokugras, *Turk. J. Biochem.*, **28**, 54 (2003).
24. A.L. Guillozet, M.-M. Mesulam, J.F. Smiley and D.C. Mash, *Ann. Neurol.*, **42**, 909 (1997).
25. C.G. Ballard and E.K. Perry, *Acta Neurol. Taiwan*, **12**, 109 (2003).
26. N.H. Greig, T. Utsuki, D.K. Ingram, Y. Wang, G. Pepeu, C. Scali, Q.-S. Yu, J. Mamczarz, H.W. Holloway, T. Giordano, D. Chen, K. Furukawa, K. Sambamurti, A. Brossi and D.K. Lahiri, *Proc. Natl. Acad. Sci. USA*, **102**, 17213 (2005).