ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2018, *63*(11), 1035-1041

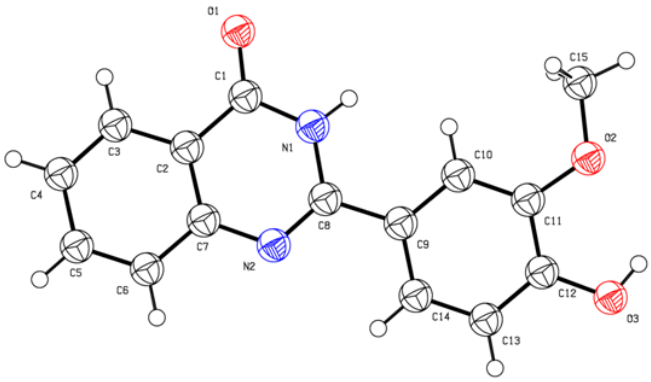
SYNTHESIS, *IN SILICO* PHARMACOKINETIC PROFILE AND ANTI-CHOLINESTERASE ACTIVITY OF QUINAZOLIN-4(*3H*)-ONE DERIVATIVES

Muhammad SARFRAZ,* Nargis SULTANA and Muhammad I. TARIQ

Department of Chemistry, University of Sargodha, Sargodha, Pakistan

Received November 24, 2017

We have carried out synthesis and biological evaluation of various quinazolin-4(3*H*)-one derivatives as potent cholinesterase (AChE/BChE) inhibitors. *In vitro* assay results revealed that all compounds exhibited inhibitory activity against both cholinesterase enzymes (AChE and BChE) and in few cases this activity was comparable to that of standard galantamine drug. Among all, the compounds **3j** with 3-methoxy-4-hydroxy groups attached to phenyl ring at C-2 position showed the highest inhibition activity with IC_{50} values of **4.2±0.13** μM and **12.7±1.44** μM for AChE and BChE, respectively. The compound **3c** with chloro group at *para* position of the phenyl ring was found to be the second most potent cholinesterase inhibitor, displaying an IC_{50} value of **6.1±1.06** μM **(**AChE**)** and **13.8±0.74** μM (BChE). Preliminary *in silico* pharmacokinetic studies showed that, with the exception of a few compounds, all others have a good pharmacokinetic profile. Analysis of molecular descriptors and drug likeliness properties by using the tool Molinspiration server showed that all synthesized compounds are in good agreement with Lipinski Rules of five. The synthesized compounds can be used as structural foundation for the preparation of new potent cholinesterase inhibitors.



INTRODUCTION

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are known to regulate various physiological functions like digestion, blood coagulation and neurotransmission by catalyzing the hydrolysis of the acetylcholine. Due to this critical role of cholinesterase, several disorders like pancreatitis, thrombosis and Alzheimer's disease (AD) are associated with their activity.[1,2] Therefore, it is necessary to control the activity of cholinesterase to reduce their side effects. AChE and BChE enzymes inhibition increases ACh level, which can interact with neuronal receptor and ultimately reduces symptoms of AD and other neurotransmission disorders.[3] Cholinesterase inhibitors have been used in the various conditions such as type 2 diabetes and chronic pain other than in the management of myasthenia gravis, senile dementia, ataxia, Parkinson's disease and AD.[4-7] Moreover, different classes of cholinesterase inhibitors such as tacrine, rivastigmine, donepezil, xanthostigmine, galantamine, *para*-aminobenzoic acid, flavonoid, coumarin, and pyrrolo-isoxazole analogues have been developed and studied.[8]

Although various chemical moieties have shown anti-ChE potential, however, different heterocyclic compounds and their derivatives have

* Corresponding author: sarfrazzed@gmail.com

proven as the most potent dual cholinesterase inhibitors. Many synthetic nitrogen heterocyclic moieties are well known to display a wide range of biological activities like antibacterial, antiviral, anti-inflammatory, antifungal, antioxidants, analgesics, anticancer, sedatives, anticonvulsants and hypnotics, etc. Due to this reason, more than 75% structural assemblies of top 200 branded drugs available in the market are made up of heterocyclic fragments.[9-10] Various simple and hybrid aromatic heterocyclic and *N*-heterocyclic moieties including imidazolidines, oxazolidines and benzoxazoles analogues have been studied for anticholinesterase potency.[11-14]

Quinazolines, a class of fused pyrimidine heterocyclic compounds, have displayed a wide range of biological activities like antimicrobial, anticonvulsant, hypnotic, anticancer, antihistaminic, anti-inflammatory, diuretic, antimalarial, anti-hypertensive, antifungal, analgesic, antagonism of ghrelin receptor and COX-2 inhibitory activities.[15-19] In addition, some researchers also reported the biological potential of quinazoline-containing compounds as inhibitors of AChE and BChE.[20-21]

Recently, our research group has reported synthesis and biological activity of various imine and 2,3-dihydroquinazolin-4(*1H*)-one derivatives such as urease and cholinesterase inhibitors.[22-25] In our present project, we have replaced ketones with aromatic aldehydes in order to obtain balance between hydrophilic and hydrophobic sites. The objective of this study was to develop quinazolin-4(3*H*)-one derivatives as potent dual cholinesterase (AChE/BChE) inhibitors.

RESULTS AND DISCUSSION

Synthesis and Characterization

Various synthetic strategies have been used to obtain diversified quinazoline derivatives by adopting traditional condensation procedures, using different metals such as iridium, rhodium and palladium and employing other catalytic methodologies such as domino reaction, catalytic carbonylation and hydrogen transfer process.[26-28] However, drastic reaction conditions, prolonged reaction time, low yield and use of sophisticated research methodologies were the main concerns. We tried a relatively inexpensive acid catalysis method for the synthesis of 2-substituted-quinazolin-4(3*H*)-one from the reaction of anthranilamide and aromatic aldehydes under acid catalysis reaction conditions with excellent yield (**Scheme 1**). The nature and position of the substituents have been displayed in **Table 1**. In our previous study, a racemic mixture was obtained. Conversely, in the current project, an enantiomeric[24] pure product was obtained.

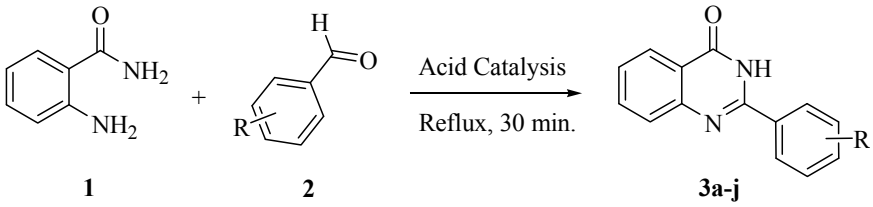
Assignment of peaks in ^{1}HNMR spectra of **3a-l**, was based on ^{1}H signals of each proton, chemical shift values and coupling constants in aromatic and aliphatic regions. Un-substituted phenyl ring of quinazoline was characterized by four ^1H signals as dd (J_{ortho} = 8 Hz and J_{meta} = 2 Hz), triplet (J_{ortho} = 8 Hz), multiplet and doublet (J_{ortho} = 8 Hz) for protons H-5, H-6, H-7 and H-8 respectively. A broad singlet at 7.91-7.93 ppm was assigned to –N*H* proton in the position-3 of the quinazoline ring. The structure of the synthesized compounds was also confirmed by single beam X-ray diffraction studies.

Suitable crystals of the synthesized compounds were grown in ethyl acetate and ethanol mixture (1:1) and XRD analysis data confirmed the structure of the synthesized compounds. An ORTEP diagram of the representative compound **3j** is shown in **Figure 1.**

In vitro pharmacology: AChE and BChE inhibition assay

All synthesized quinazoline derivatives were tested for their anti-cholinesterase (AChE and BChE) activity and the results were compared with standard drug galantamine. The *in vitro* assay results as inhibitory potency (IC_{50} values) and the selectivity index (**Table 1)** showed that all tested compounds exhibited good to moderate degree of inhibition.

Generally, all quinazoline derivatives having chloro, bromo, methoxy and hydroxy groups attached to *para* position of C-2 phenyl ring (**3c**, **3e**, **3g, 3i** and **3j**) displayed better AChE/BChE inhibitory activity as compared to other listed compounds. Among all, the compound **3j** having both 3-methoxy- and 4-hydroxy- groups attached to phenyl ring at C-2 position showed the highest inhibition activity toward tested enzymes (AChE/BChE), whereas the compound **3c** with chloro group at *para* position of the phenyl ring at C-2 position was the second most potent cholinesterase inhibitor displaying IC_{50} value of **6.1±1.06** μM **(**AChE**)** and **13.8±0.74** μM (BChE). Overall, the compound **3j** with IC_{50} values of **4.2±0.13** μM and **12.7±1.44** μM for AChE and BChE, respectively, and selectivity index of 3.0 can be considered as leading cholinesterase inhibitor (AChE/BChE).



1 **2** **3a-j**

Scheme 1 – Synthesis of 2-substituted quinazolin-4(3*H*)-ones (**3a-j**).

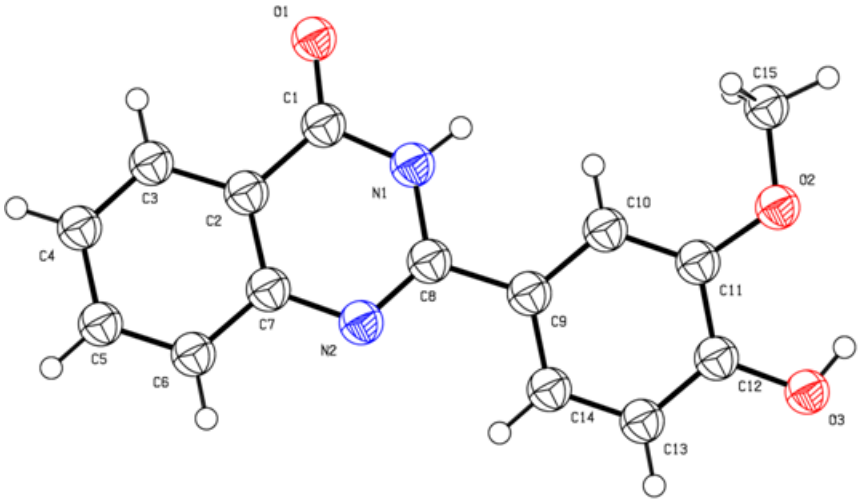


Fig. 1 – ORTEP diagram of compound **3j** (CCDC No. 1577082).

Table 1

In vitro cholinesterase inhibitory activity of the synthesized compounds

Compounds	R	IC_{50} (μM ±SEM)[a]		SI [b]
		eeAChE	eqBChE	
3a	$N(CH_3)_2$	97.3±1.01	123.4±1.44	1.3
3b	2-Cl	59.5±1.40	79.1±1.22	1.3
3c	4-Cl	**6.1±1.06**	**13.8±0.74**	1.6
3d	2-Br	44.4±1.13	72.4±0.62	2.1
3e	4-Br	8.4±0.28	23.4±1.66	1.6
3f	3-OCH_3	27.5±0.10	75.2±1.13	2.7
3g	4-OCH_3	17.3±1.82	44.6±1.36	2.6
3h	3-OH	23.4±1.18	35.1±0.23	1.5
3i	4-OH	13.2±1.42	26.2±1.30	2.0
3j	3- OCH3, 4-OH	**4.2±0.13**	**12.7±1.44**	3.0
3k	2-NO_2	43.4±1.05	84.1±1.23	1.9
3l	4-NO_2	23.2±0.42	46.1±0.90	2.0
Galantamine		**4.0 ± 0.10**	**15.0 ± 0.67**	**3.7**

[a]Values are expressed as mean (standard error of the mean of at least three experiments).
[b] Selectivity Index (SI) = IC_{50} ratio (BChE/AChE).

Preliminary *in silico* pharmacokinetic

In the past, the lack of efficacy and unacceptable toxicity were two main causes of the high failure rate of drug candidates at the clinical trial stage and it is estimated that about 50% of potential therapeutic candidates failed in clinical trials due to poor ADMET properties and unacceptable side effects. So, pharmacokinetic study played an important role in the development of the synthesized compound as an effective drug.[29] An experimental evaluation of ADMET

profiles is time consuming as well as costly. Therefore, the importance of *in silico* pharmacokinetic study was heightened.

admetSAR prediction

ADME is an important concept that describes potential impact that a compound or drug may have on a living system in the context of cell biology and biochemistry. ADME is generally used to describe the impact of a drug or pharmaceutical compound.

ADMET results showed that all synthesized derivatives are predicted to display penetration across the blood-brain barrier (BBB), absorbed in the human intestine, have non AMES toxicity (AT) and non-carcinogenicity except for compounds **3a, 3f, 3g, 3j, 3k** and **3l,** which showed AT. All AMES toxic compounds possess amine, methoxy and nitro groups attached to phenyl ring at C-2 position. Comparison of the calculated probabilities with standard drug galantamine showed that except for a few compounds, all others have good probabilities for penetration across BBB, human intestinal absorption (HIA), non AT and non-carcinogenicity as shown in **Table 2**.

Molinspiration calculation

The molecular descriptors of synthesized compounds as per Lipinski's rule of five showed that all quinazoline derivatives have molecular weight in the range of 238-301. The therapeutic drug action is reversibly linked to the molecular weight of the compound. It has been found that low molecular weight drug molecules (<500) are easily diffused, absorbed and transported compared to bulky molecule weight compounds[30]. Moreover, calculated data showed that the number of hydrogen bond donors (NH and OH) and acceptors (O and N atoms) in all of the tested compounds ranged from 1-2 & 3-6 which were in close agreement with the Lipinski's limit range of less than 5 and 10 respectively. Topological Polar Surface Area (TPSA) and lipophilicity (log *P* value) values are helpful in predicting oral bioavailability and penetration through biomembranes of the synthesized drug molecules.[31] Calculated log P value of synthesized compounds varied from 2.44 to 3.91 (<5), whereas TPSA values were predicted in the range of 45.75 to 91.58 which indicate good bioavailability by oral route. The molecular descriptors of all compounds are given in **Table 3.**

Table 2

Comparison of calculated ADMET probabilities

Sample Code	BBB		HIA		AMES Toxicity		Carcinogen	
	Results	**Probability**	**Results**	**Probability**	**Results**	**Probability**	**Results**	**Probability**
Galantamine	BBB+	0.9412	HIA+	0.9235	Non AT	0.7282	Non-carcinogen	0.9377
3a	BBB+	0.9694	HIA+	0.9973	AMES toxic	0.6743	Non-carcinogen	0.8991
3b	BBB+	0.9896	HIA+	1.0000	Non AT	0.6409	Non-carcinogen	0.9368
3c	BBB+	0.9896	HIA+	1.0000	Non AT	0.6409	Non-carcinogen	0.9368
3d	BBB+	0.9887	HIA+	1.0000	Non AT	0.6239	Non-carcinogen	0.9478
3e	BBB+	0.9887	HIA+	1.0000	Non AT	0.6239	Non-carcinogen	0.9478
3f	BBB+	0.9854	HIA+	1.0000	AMES toxic	0.6390	Non-carcinogen	0.9524
3g	BBB+	0.9854	HIA+	1.0000	AMES toxic	0.6390	Non-carcinogen	0.9524
3h	BBB+	0.9669	HIA+	1.0000	Non AT	0.7314	Non-carcinogen	0.9290
3i	BBB+	0.9669	HIA+	1.0000	Non AT	0.7314	Non-carcinogen	0.9290
3j	BBB+	0.7717	HIA+	1.0000	AMES toxic	0.6079	Non-carcinogen	0.9406
3k	BBB+	0.9729	HIA+	0.9968	AMES toxic	0.8779	Non-carcinogen	0.7556
3l	BBB+	0.9729	HIA+	0.9968	AMES toxic	0.8779	Non-carcinogen	0.7556

Table 3

Molinspiration calculation of the synthesized compounds

Sample Code	miLogP	TPSA	natoms	MW	nON	NONHN	nviolation	nrotb
Galantamine	1.24	62.16	23	317.38	5	2	0	1
3a	3.2	48.99	20	265.32	4	1	0	2
3b	3.78	45.75	18	256.69	3	1	0	1
3c	3.78	45.75	18	256.69	3	1	0	1
3d	3.91	45.75	18	301.14	3	1	0	1
3e	3.91	45.75	18	301.14	3	1	0	1
3f	3.16	54.99	19	252.27	4	1	0	2
3g	3.16	54.99	19	252.27	4	1	0	2
3h	2.62	65.98	18	238.25	4	2	0	1
3i	2.62	65.98	18	238.25	4	2	0	1
3j	2.44	75.22	20	268.27	5	2	0	2
3k	3.06	91.58	20	267.24	6	1	0	2
3l	3.06	91.58	20	267.24	6	1	0	2

EXPERIMENTAL

Material and Methods

All chemicals and solvents used for the synthesis work were of analytical grade and used as received. Acetylthiocholine iodide and butyrylthiocholine iodide were procured from Sigma-Aldrich UK and Sigma-Aldrich Switzerland respectively whereas purchasing of AChE (Electric eel type-VI-S, code 1001596210) and BChE (Equine serum Lyophilized, code 101292670) was done from Sigma-Aldrich GmbH USA. DTNB (code 101261619) was arranged from Sigma-Aldrich Germany and Galantamine hydrobromide Lycoris Sp. (code G1660) from Sigma-Aldrich France. Bruker DRX 400 MHz NMR spectrometer was utilized for recording ^{1}H NMR spectra and chemical shifts were reported in comparison to $SiMe_4$. Crystallization of the synthesized compounds was done by slow evaporation in a solution of ethyl acetate/ethanol (1:1) and suitable crystals of the individual compounds were analyzed on a Bruker KAPPA Apex II diffractometer with graphite-monochromatized Mo Ka radiation, λMo = 0.710 73 Å at 100 K. Data collection of representative compounds was carried out under monoclinic system with space groups C 2/c. Data reduction and structure refinement was achieved by using SAINT and SHELXL-2013 program package respectively. Standard geometrical calculations were done by using PLATON software.[32-33]

General procedure for the synthesis of 2-substituted quinazolin-4(3*H*)-ones (3a-l)

To a stirring solution of 2-amino benzamide (100 mmol) and the corresponding aldehyde (100 mmol) in DCM, drop wise addition of conc. HNO_3/ HCl (1 mL) was carried out and the resulted reaction mixture was refluxed for 30 min. Reaction progress and completion was monitored by TLC and crude product obtained after completion of the reaction was concentrated by a rotary evaporator. To concentrated product, water was added and precipitates so formed were filtered, washed with plenty of water and oven dried. Subsequently, recrystallization of the synthesized product with ethyl acetate/ethanol (1:1) afforded crystals of 2-substituted quinazolin-4(3*H*)-one.

Synthesis of 2-(4-dimethylamino-phenyl)-3H-quinazolin-4-one (3a)

Compound **3a** was synthesized from 2-amino benzamide and 4-dimethylamino-benzaldehyde by following the general procedure**.** The resulted white crystalline solid (81.5% yield) was characterized by m.p. 361-362 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.93 (s, 1H, N*H*), 7.86 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.59-7.54 (m, 1H, Ar*H*), 7.44-7.40 (m, 2H, Ar*H*), 7.34 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 2H, Ar*H*), 6.65 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 2H, Ar*H*), 2.78 (s, 6H, 2×CH_3) ppm.

Synthesis of 2-(2-chloro-phenyl)-3H-quinazolin-4-one (3b)

Synthesis of compound **3b** was done by adopting general procedure from a mixture of 2-amino benzamide and 2-chloro benzaldehyde. A white crystalline solid (78.2% yield) was obtained and characterized by m.p. 340-341 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (s, 1H, N*H*), 7.89 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.62-7.58 (m, 2H, Ar*H*), 7.54 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.44-7.4.39 (m, 2H, Ar*H*), 7.32 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.25-7.21 (m, 1H, Ar*H*), 7.15-7.11 (m, 1H, Ar*H*).

Synthesis of 2-(4-chloro-phenyl)- 3H-quinazolin-4-one (3c)

Synthesis of **3c** was carried out by using general procedure from a mixture of 2-amino benzamide and 4-chloro benzaldehyde. The resulted white crystalline solid (89.0% yield) was characterized by m.p. 338-339 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (s, 1H, N*H*), 7.87 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.60-7.56 (m, 1H, Ar*H*), 7.51 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 2H, Ar*H*), 7.44-7.40 (m, 2H, Ar*H*), 7.26 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 2H, Ar*H*) ppm.

Synthesis of 2-(4-methoxy-phenyl)-3H-quinazolin-4-one (3g)

The compound **3g** was obtained from the reaction of 2-amino benzamide and 4-methoxy benzaldehyde by following the general reaction procedure. The obtained white crystalline solid (86.7% yield) was characterized by m.p. 347-348 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.91 (s, 1H, N*H*), 7.88

(dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.60-7.56 (m, 1H, Ar*H*), 7.50 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 2H, Ar*H*), 7.45-7.40 (m, 2H, Ar*H*), 6.81 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 2H, Ar*H*), 3.71 (s, 3H, CH_3) ppm.

***Synthesis of 2-(4-hydroxy-phenyl)-3H-quinazolin-4-one* (3i)**

Synthesis of the compound **3i** was achieved from a mixture of 2-amino benzamide and 4-hydroxy benzaldehyde by adopting the general procedure. Characterization of the so-obtained white crystalline solid (80.8% yield) was carried out by m.p. 406-407 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.93 (s, 1H, N*H*), 7.89 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.60-7.55 (m, 1H, Ar*H*), 7.48-7.44 (m, 2H, Ar*H*), 7.40 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 2H, Ar*H*), 6.78 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 2H, Ar*H*), 5.31 (s, 1H, OH) ppm.

***Synthesis of 2-(4-hydroxy-3-methoxy-phenyl)-3H-quinazolin-4-one* (3j)**

The compound **3j** was synthesized by the reaction of 2-amino benzamide with 4-hydroxy-3-methoxy benzaldehyde by using the general procedure. A white crystalline solid (79.4% yield) was obtained and characterized by m.p. 458-459 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (s, 1H, N*H*), 7.88 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.60-7.55 (m, 1H, Ar*H*), 7.48-7.44 (m, 2H, Ar*H*), 7.09 (d, ^3J = 8 Hz, 1H, Ar*H*), 6.94 (s, 1H, Ar*H*), 6.63 (d, ^3J = 7 Hz, 1H, Ar*H*), 5.10 (s, 1H, OH), 3.76 (s, 3H, CH_3) ppm.

***Synthesis of 2-(4-nitro-phenyl)-3H-quinazolin-4-one* (3l)**

The compound **3l** was synthesized from a mixture of 2-amino benzamide and 4-nitro benzaldehyde by following the general reaction procedure. The resulted light yellow solid (72.1% yield) was characterized by m.p. 401-402 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = δ =8.19 (d, ^3J = 8 Hz, 2H, Ar*H*), 7.92 (s, 1H, N*H*), 7.89 (dd, ^3J = 8 Hz, ^4J = 2 Hz, 1H, Ar*H*), 7.79 (d, ^3J = 7 Hz, 2H, Ar*H*), 7.60-7.55 (m, 1H, Ar*H*), 7.46-7.42 (m, 2H, Ar*H*) ppm.

Determination of AChE and BChE inhibitory activity

All synthesized compounds were subjected to anti-cholinesterase activity study in accordance with Ellman's methodology.[34] Tested compound was dissolved in 0.1 M phosphate buffer (KH_2PO_4/K_2HPO_4) having pH 8.0. To this solution, an appropriate amount of Ellman's reagent (DTNB) and 0.03 U/mL of enzymes (AChE and BChE) were added and this reaction mixture was pre-incubated at 30 °C for 10 min. After pre-incubation, 1mM of ATCI or BTCI was added to the reaction mixture and incubated again for 15 min. Monitoring of the enzymatic hydrolysis was done at 412 nm by using a μQuant microplate spectrophotometer (MQX200, BioTek USA). Enzyme inhibition percentage was plotted against the sample concentrations to obtain IC_{50} values of all tested compounds. All reactions were carried out in triplicate and reference drug used was galantamine.

Determination of *in silico* pharmacokinetic properties

ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of synthesized compounds were predicted by using online ADMET structure-activity relationship server, known as admetSAR.[35] Online *admet*SAR server was used to carry out *in silico* ADMET predictions of the synthesized compounds including penetration across BBB, HIA, AT and carcinogenicity. SMILES files of the synthesized compounds were used to predict ADMET properties in comparison to standard drug galantamine. Analysis of molecular descriptors and drug likeliness properties of the synthesized compounds was carried out by using the tool Molinspiration server (http://www.molinspiration.com) which is based on Lipinski Rules of five.[36] As per this rule, if a molecule has molecular weight ≤ 500, log $P \leq 5$, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5 then this molecule can be considered as the most "druglike" molecule. A molecule is considered to create problems with oral bioavailability if this molecule violates more than one of these rules.

CONCLUSION

We have synthesized and biologically evaluated several quinazoline-4(3*H)*-one derivatives for AChE and BChE inhibitory potency and found that all these derivatives are active against both enzymes in the micromolar range. *In vitro* assay results revealed that the compound **3c** with chloro group at *para* position of the phenyl ring at C-2 position is the lead compound, displaying an IC_{50} value of **6.1±1.06** μM **(**AChE**)** and **13.8±0.74** μM (BChE). However, the replacement of chloro with hydroxy and hydrogen at position-3 with methoxy group at phenyl ring of C-2 position even enhanced inhibition activity and the resulted compounds **3j** with IC_{50} values of **4.2±0.13** μM and **12.7±1.44** μM for AChE and BChE respectively can be considered the most potent dual cholinesterase inhibitor as compared to standard drug Galantamine. Preliminary *in silico* pharmacokinetic studies by using online *admet*SAR and molinspiration servers showed that excepting few compounds all others have good pharmacokinetic profile. The findings of the present study suggest that appropriate structural modification of quinazoline scaffold may furnish potential AChE or BChE inhibitors.

Acknowledgments. Authors are thankful to Higher Education Commission (HEC), Pakistan for financial support. Authors are also thankful to Prof. Dr. Muhammad Nawaz Tahir, University of Sargodha, Pakistan for XRD studies and Dr. Abdul Sadiq, University of Malakand, Pakistan for biological activity study.

REFERENCES

1. D. C. Whitcomb and M. E. Lowe, *Dig. Dis. Sci.*, **2007**, 52, 1-17.
2. M. Pohanka, *Biomed. Pap.*, **2011**, *155*, 219-223.
3. R. M. Lane, S. G. Potkin and A. Enz, *Int. J. Neuropsychopharmacol.*, **2006**, *9*, 101-124.
4. B. M. McGleenon, K. B. Dynan and A. P. Passmore, *Br. J. Clin. Pharmacol.*, **1999**, *48*, 471-480.

5. M. M. Mehndiratta, S. Pandey and T. Kuntzer, *Cochrane Database Syst. Rev.*, **2011**, *2*. CD006986
6. M. A. Kamal, Y. Tan, J. P. Seale and X. Qu, *Neurochem. Res.,* **2009**, *34*, 2163-2169.
7. A. Folkesson, P. H. Honoré, L. M. Andersen, P. Kristensen and O. J. Bjerrum, *J. Neural Transm.*, **2010**, *117*, 1377-1385.
8. P. Anand and B. Singh, *Arch. Pharmacal Res.*, **2013**, *36*, 375-399.
9. J. A. Joule and K. Mills, "Heterocyclic chemistry at a glance", John Wiley & Sons, 2nd Edition, 2012.
10. Y. Ju and R. S. Varma, *J. Org. Chem.*, **2006**, *71*, 135-141.
11. S. Ahmad, F. Iftikhar, F. Ullah, A. Sadiq and U. Rashid, *Bioorg. Chem.*, **2016**, *69*, 91-101.
12. A. Basiri, V. Murugaiyah, H. Osman, R. S. Kumar, Y. Kia and M. A. Ali, *Bioorg. Med. Chem.*, **2013**, *21*, 3022-3031.
13. D. P. Sangi, J. L. Monteiro, K. L. Vanzolini, Q. B. Cass, M. W. Paixão and A. G. Corrêa, *J. Braz. Chem. Soc.*, **2014**, *25*, 887-889.
14. H. Zhi, L. M. Chen, L. L. Zhang, S. J. Liu, D. C. C. Wan, H. Q. Lin and C. Hu, *Arkivoc*, **2008**, *13*, 266-277.
15. N. M. A. Gawad, H. H. Georgey, R. M. Youssef and N. A. El Sayed, *Med. Chem. Res.*, **2011**, *20*, 1280-1286.
16. P. M. Chandrika, T. Yakaiah, A. R. R. Rao, B. Narsaiah, N. C. Reddy, V. Sridhar and J. V. Rao, *Eur. J. Med. Chem.*, **2008**, *43*, 846-852.
17. E. Cohen, B. Klarberg and J. R. Vaughan Jr, *J. Am. Chem. Soc.*, **1960**, *82*, 2731-2735.
18. H. Kikuchi, K. Yamamoto, S. Horoiwa, S. Hirai, R. Kasahara, N. Hariguchi and Y. Oshima, *J. Med. Chem.*, **2006**, *49*, 4698-4706.
19. A. M. E. Mohsen, S. Omar, A. S. El-Din, M. L. Ibrahim and A. A. El-Tombary, *Alex. J. Pharm. Sci.*, **1991**, *5*, 213-215.
20. Z. Li, B. Wang, J. Q. Hou, S. L. Huang, T. M. Ou, J. H. Tan and Z. S. Huang, *J. Enzyme Inhib. Med. Chem.*, **2013**, *28*, 583-592.
21. M. Uraz, S. Karakuş, U. A. Mohsen, Z. A. Kaplancıklı and S. Rollas, *Marmara Pharm .J.*, **2017**, 21, 96-101.
22. M. Sarfraz, S. Ahmad, M. I. Tariq and M. N. Qiser, *Iran. J. Sci. Technol. Trans. Sci.*, **2018,** 1-9. https://doi.org/10.1007/s40995-018-0603-z.
23. M. Sarfraz, N. Sultana, M. Jamil and M. I. Tariq, *Rev. Roum. Chim*., **2018**, 63, 227-234.
24. M. Sarfraz, N. Sultana, U. Rashid, M. S. Akram, A. Sadiq and M. I. Tariq, *Bioorg. Chem.*, **2017**, *70*, 237-244.
25. N. Sultana, M. Sarfraz, S. T. Tanoli, M. S. Akram, A. Sadiq, U. Rashid and M. I. Tariq, *Bioorg. Chem.*, **2017**, *72*, 256-267.
26. T. M. M. Maiden and J. P. A. Harrity, *Org. Biomol. Chem.*, **2016**, *14*, 8014-8025.
27. J. F. Liu, J. Lee, A. M. Dalton, G. Bi, L. Yu, C. M. Baldino and M. Brown, *Tetrahedron Lett.*, **2005**, *46*, 1241-1244.
28. B. Q. Hu, L. X. Wang, J. F. Xiang, L. Yang and Y. L. Tang, *Chin. Chem. Lett.*, **2015**, *26*, 369-372.
29. I. Kola and J. Landis, *Nat. Rev. Drug Discov.*, **2004**, *3*, 711-716.
30. V. Srimai, M. Ramesh, K. S. Parameshwar and T. Parthasarathy, *Med. Chem. Res.*, **2013**, *22*, 5314-5323.
31. L. C. Chang, R. F. Spanjersberg, J. K. von Frijtag Drabbe Künzel, T. Mulder-Krieger, G. van den Hout, M. W. Beukers, J. Brussee and A. P. IJzerman, *J. Med. Chem.*, **2004**, *47*, 6529-6540.
32. G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, **2008**, *64*, 112-122.
33. Siemens, "SAINT: Area-Detector Control and Integration Software". *Siemens Analytical X-ray Instruments Inc., Madison, WI, USA*, 1995.
34. G. L. Ellman, K. D. Courtney, V. Andres and R. M. Featherstone, *Biochem. Pharmacol.,* **1961**, *7*, 88IN191-9095.
35. F. Cheng, W. Li, Y. Zhou, J. Shen, Z. Wu, G. Liu and Y. Tang, *J. Chem. Inf. Model.,* **2012**, *52*, 3099-3105.
36. C. A. Lipinski, *Drug Discov. Today: Technol.*, **2004**, *1*, 337-341.