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Ultrasound One Pot Synthesis of Fused Quinazolinones and Quinazolinediones, Screening and Molecular Docking Study as Phosphodiesterase 7A Inhibitors

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PHOSPHODIESTERASE 7A enzyme is one of the most recent targets for designing potent anti-inflammatory agents with minimal side effects. Quinazolinones are unique building blocks of wide biological activities. Different quinazolinones were reported to act as Phosphodiesterase 7A inhibitors anti-inflammatory particularly against chronic inflammation and autoimmune disease. Ultrasound is a green convenient method for synthesis of different heterocyclic ring system that is advantageous in terms of yield and reaction time. Ultrasound was used for one pot synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a] quinazolin-5,11-diones and 3-arylquinazolin-2,4(1*H*,3*H*)-diones. Seventeen compounds were synthesized in good yields. The synthesized compounds were inspected for in vitro inhibitory activity against phosphodiesterase7A enzyme. Molecular docking was used to study the mode of interaction of all the synthesized compounds into the enzyme phosphodiesterase 7A binding site. Five compounds showed high inhibitory activity of enzyme Phosphodiesterase 7A at micro-molar level compared to reference drug. The compounds showed good recognition at the enzyme binding site in the molecular docking. There was a good agreement between the molecular docking and the biological screening results.

Keywords: Docking Study, Phosphodiesterase 7A inhibitory assay, In vitro screening, Quinazolinedione, Dihydroisoindoloquinazolinone.

Introduction

Quinazolinones and their fused derivatives are scaffolds for wide range of biological activities. Altering substituents as well as their position on the ring had a great influence on the activity[1]quinazolinones were reported to act as anti-inflammatory, [2-5]anti-ulcerative, [6] antifungal, [7,8]anticancer, [9-11]anti-tuberculosis, [12]anticonvulsant, [13]antimicrobial, [14-16]antibacterial, [17-19]antiviral, [20]anti-parkinsonian, [21]antihypertensive, [5,22,23] antidepressant, [24] anti-malarial, [25]anti-rheumatic, [26]and anti HIV[27]. Ultrasound provides exceptional conditions of elevated temperature and pressure that is superior to traditional chemistry in yields and reaction times. Sonochemistry offers rapid ecofriendly more convenient method for synthesis of a variety of heterocycles and fused heterocycles[28]. One-pot synthesis or multi-component reactions are multi-step reactions that take place without separation of intermediates to put together three or more building blocks of known functionality in order to be combined in a product carrying features of all the reactants. Such reactions are easy, practicable, efficient and are mostly performed in eco-friendly conditions[29-31]. Selective inhibitors

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of c-AMP-specific PDEs (cyclic Adenosine monophosphate specific Phosphodiesterases) are documented to play a role in the regulation and control of immune disorders such as multiple sclerosis and inflammatory processes,[32]. as well as, disorders of the central nervous system (CNS) [33, 34]. PDE7 (phosphodiesterase 7) is one of c-AMP- specific enzymes that has two members (PDE7A and PDE7B). PDE7A1 inhibitors to have ability to enhance neuroprotection and diminish neuro inflammation, with minimal side effects that are re-counted with earlier classes of Phosphodiesterase[35-37]. There are different classes of PDE7A1 inhibitors. Benzothiadiazine and benzothienothiadiazine derivatives, constituted the first described heterocyclic family of compounds with PDE7 inhibitory properties. Spiroquinazolinones, sulfonamide and thiadiazole analogs have been described as PDE7 inhibitors [38-40]. Dihydronaphthyridin- 2,8-dione derivatives were reported to show potent and selective inhibition of PDE7[41]. Isothiazole and isoxazole fused pyrimidines showed some potency as PDE7 inhibitorsas well, [42] Thienopyrimidinones, [43] benzothienothiadiazine, [39] and Thioxoquinazoline derivatives showed potent in vitro inhibition of PDE7A1[44]. Different series of biphenyl-4-methylsulfanylquinazoline derivatives were reported as PDE7A1 inhibitors[45]. Redondo [46]reported a variety of quinazoline derivatives as PDE7 inhibitors and studied their SAR and ability to act as neuroprotective agents. Based in the previous literature, the goal of this work is to design and synthesis new quinazoline derivatives to inspect their PDE7A1 inhibitory activity and binding mode at the enzyme binding site.

Experimental

Melting points were recorded on Stuart melting apparatus. IR spectra (KBr) were recorded on a FT-IR spectrometer (ν cm^{-1}). Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on Bruker 400 MHz and 300 MHZ spectrometer using DMSO-d_6 or $CDCl_3$ as solvents; the chemical shifts are expressed in δ ppm using TMS as internal standard. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were performed in Faculty of Science, King Abdulaziz University. Mass spectra were recorded on shimadzu QP-GC/MS mass spectrometers at microanalytical unit faculty of science Cairo university. Elemental microanalyses were carried out, and the results were within ±0.3 from the theoretical values. Solvent evaporation was performed under reduced pressure using Buchi R-3000 Rotacool Rotatory Evaporator, thin layer chromatography was performed on pre-coated (0.25 mm) silica gel GF254 plates (E. Merck, Germany); compounds were detected with 254 nm UV lamp. All chemicals and starting materials were commercial chemicals obtained from sigma-Aldrech.

Chemistry

- *General procedure for Synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a]quinazolin-5,11-diones(4–13)*

The title compounds were prepared by two methods; Method A:A mixture of 5-haloisatoicanhydrides1a,b (1mmol), 2-formylbenzoic acid (2) (1 mmol) and proper amine 3a-e (1 mmol) in ethanol (20 ml) and montomorillonite K10 (10%w/w)were subjected to ultrasound irradiation at 80°C for suitable time. Method B:A mixture of 5-haloisatoicanhydride 1a,b(1 mmol), 2-formylbenzoic acid (2) (1 mmol) and proper amine 3a-c (1 mmol) in acetic acid (30 ml) were subjected to ultrasound irradiation at 80°C for suitable time. In both methods, the reactionwas monitored by TLC till the starting materials were no longer detectable by TLC, the mixture was allowed to cool then poured on crushed ice. The formed precipitate was filtered off and recrystallized from aqueous ethanol (96%) to afford the corresponding3-substituted 6-aryldihydroisoindolo[2,1-a]quinazolin-5,11-diones 4-13. The synthesized compoundswith their physical data are listed below.

3-Bromo-6-(2-methoxybenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (4)

Yield: 87%, mp: 112-114°C, IR (KBr, cm^{-1}): 1765 and 1696 (C=O). ^1H NMR (300Hz, DMSO-d_6): δ 7.98 (s,1H, C-4-H), 7.91(d, 1H, *J*=3.0Hz, C-1-H), 7.88 (d,1H, *J*=3.2Hz, C-2-H), 7.12-7.09 (m,4H, Ar-H), 7.08-6.82 (m, 4H, Ar-H), 6.81 (s, 1H, C-6a-H), 4.53 (s, 2H, CH_2), 3.81 (s, 3H, CH_3). Mass spectrum, m/z (%):450 (0.92) M^++1, 449 (1.0) M^+, 328 (2.3), 313 (4.3), 285(1.9).

3-Chloro-6-(2-methoxybenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (5)

Yield: 89%, mp:90-92°C, IR (KBr, cm^{-1}): 1769 and 1698 (C=O). ^1H NMR (400Hz, $CDCl_3$): δ 8.17 (s, 1H, C-4-H), 8.11 (d, 1H,*J*=2.4 Hz, C-1-H), 8.09 (d,1H,*J*=2.4Hz, C-2-H), 8.07 (d, 1H, Ar-H), 7.97 (d, 1H, Ar-H), 7.95 (d,1H, Ar-H), 7.94 (dd, 1H, *J*=2.4Hz, Ar-H), 7.62 (d, 1H, *J*=2.8Hz, Ar-H), 7.60 (d, 1H, *J*=2.4Hz, Ar-H), 7.52 (d, 1H,

Ar-H), 7.09 (d, 1H, *J*= 2.8Hz, Ar-H), 6.99 (s,1H, C-6a-H), 4.80 (s, 2H, CH_2), 3.88 (s,3H, CH_3). Mass spectrum, m/z (%):406 (0.05) M^++2, 404 (0.13)M^+, 374 (0.09), 283 (0.2), 269(1.4).

3-Bromo-6-(4-methoxybenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (6)

Yield: 95%, mp:187-189°C, IR (KBr, cm^{-1}): 1767 and1699 (C=O). ^{1}H NMR (400Hz, $CDCl_3$): δ 8.33 (s, 1H,C-4-H), 8.02 (d,1H, *J*= 6.5Hz, C-1-H), 7.97 (d,1H, *J*=6.4Hz,C-2-H), 7.75 (dd,1H, J_1=6.4Hz, J_2=2.2Hz,Ar-H), 7.58 (m, 2H, Ar-H), 7.47 (d,1H, *J*=6.6Hz, Ar-H), 7.10 (d, 2H, *J*= 8.4Hz, Ar-H), 6.8 (d, 2H, *J*=8.4Hz,Ar-H), 6.30 (s, 1H,C-6a-H), 4.11 (d, 1H, *J*=7.1Hz,CH_2), 4.09 (d, 1H, *J*= 7.1Hz,CH_2), 3.77 (s, 3H,CH_3).^{13}C NMR (400HZ, $CDCl_3$): δ 46.2, 55.3, 70.5, 114.5, 118.5, 121.8, 121.9,122.3, 124.1, 125.1, 125.6, 127.6, 127.7, 130.8,132.2,132.4, 132.8, 135.8, 136.5, 137.6, 158.8, 162.9, 164,8.Mass spectrum, m/z (%):450 (1.7) M^++1, 449 (1.8) M^+,425 (9.3), 313 (7.9).

Chloro-6-(4-methoxybenzyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (7)

Yield: 95%,mp:85-87°C, IR (KBr, cm-1): 1767 and 1700 (C=O). ^{1}H NMR (400Hz, $CDCl_3$): δ 8.17 (d, 1H, *J*= 2.4, C-4-H), 8.07 (d,1H, *J* =8.6Hz, C-1-H), 7.96 (dd, 1H, J_1 =8.3Hz, J_2 =2.6Hz, C-2-H), 7.60 (m,4H, Ar-H), 7.10 (d, 2H, *J*=8.6Hz, Ar-H), 6.84 (d, 2H, *J*= 8.7Hz, Ar-H), 6.30 (s,1H,C-6a-H), 4.5 (d,1H, J =7.1Hz,CH), 4.38 (d, 1H, J= 7.1Hz,CH), 3.77 (s, 3H,CH_3).^{13}C NMR (400Hz, $CDCl_3$): δ 46.2, 55.3, 70.6, 113.9, 121.6, 121.7, 125.1, 125.5, 127.7, 129.1, 129.2, 129.3, 129.6, 130.6, 131.0, 132.4, 132.8, 133.6, 135.3, 137.6, 158.8, 163.09, 164.8. Mass spectrum, m/z (%):406 (1.1) M^++2, 404 (3.6) M^+, 375 (1.0), 269 (100), 121(30).

3-Bromo-6-phenyl-6,6a-dihydroisoindolo[2,1-a] quinazolin-5,11-dione (8):

Yield: 94%, mp:220-222°C, IR (KBr, cm^{-1}): 1753 and1657 (C=O), ^{1}H NMR (400 Hz, $CDCl_3$): δ 8.29 (s, 1H, C-4-H), 8.10 (d, 1H, C-1-H), 7.93 (d, 1H, C-2-H), 7.90-7.71 (m, 4H, Ar-H), 7.63-7.50 (m, 5H, Ar-H), 6.61 (s, 1H, C-6a-H).Mass spectrum, m/z (%):405 (36.0) M^++1, 404 (37.2) M^+, 377 (8.9), 133 (51.5).

3-Chloro-6-phenyl-6,6a-dihydroisoindolo[2,1-a] quinazoline-5,11-dione (9)

Yield: 95%, mp:225-227°C, IR (KBr, cm^{-1}): 1752 and 1657 (C=O). ^{1}H NMR (400Hz, $CDCl_3$): δ 8.14 (s,1H, C-4-H) ,8.10 (d, 1H, *J*=2.3Hz, C-1-H), 7.95(d,1H, *J*=2.2Hz, C-2-H) 7.90(d, 1H, *J*= 7.5Hz, Ar-H), 7.88 (d,1H, *J*=7.5Hz, Ar-H), 7.71 (m,2H, Ar-H), 7.58 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.50 (m, 1H, Ar-H), 6.35 (s, 1H, C-6a-H).^{13}C NMR (400 Hz, $CDCl_3$): δ 72.0, 110.5, 111.6, 113.7, 115.34, 119.8, 120.9,122.4, 123.2, 124.2, 126.5, 127.2, 129.2, 129.8, 130.8, 132.4, 133.6, 133.9, 134.4, 160.1, 165.2.Mass spectrum, m/z (%):362 (4.2) M^++2, 360 (11.9) M^+,257 (7.8), 105(16.8).

3-Bromo-6-(1-phenylpropyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (10)

Yield: 86%, mp:192-194°C, IR (KBr, cm^{-1}): 1770 and1697 (C=O).Mass spectrum, m/z (%):447 (0.80) M^++1, 446 (0.86) M^+,303 (8.2), 284(36.8).133(97.8).

3-Chloro-6-(1-phenylpropyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (11)

Yield: 88%, mp:212-214°C, IR (KBr, cm^{-1}): 1769 and 1699 (C=O). ^{13}C NMR (400Hz, $CDCl_3$): δ 14.8, 39.6, 55.4, 70.6, 110.3, 111.0, 113.3, 115.4, 119.7, 120.7,122.3, 123.5,124.1, 126.2, 127.1, 128.9, 129.8,130.2, 132.7, 135.4, 136.6, 139.3, 157.6, 163.0. Mass spectrum, m/z (%):404 (0.13) M^++2, 402 (0.41) M^+,290 (100), 258 (92.6), 127(53.7).

3-Bromo-6-(4-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (12)

Yield: 97%, mp:240-242°C, IR (KBr, cm^{-1}) 1753 and 1659, (C=O). ^{1}H NMR (300Hz, DMSO-d_6): δ 7.93 (s, 1H, C-4-H), 7.81 (d, 1H, C-1-H),7.73(d,1H, C-2-H),7.70-7.42(m, 4H, Ar-H) 7.39 (m, 1H, Ar-H),7.31(m,1H, Ar-H),7.28 (m,1H, Ar-H) 7.24 (m, 1H, Ar-H), 6.78 (s, 1H, C-6a-H). Mass spectrum, m/z (%):439 (79.1) M^+,438 (100), 411 (35.4), 337(17.8).

3-Chloro-6-(4-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazolin-5,11-dione (13)

Yield: 95%, mp:242-244°C, IR (KBr, cm^{-1}) 1753 and1661 (C=O). ^{1}H NMR (300Hz, DMSO-d_6): δ 7.93 (s,1H, C-4-H), 7.74 (d, 1H,*J*= 8.7Hz, C-1-H), 7.69 (d, 1H, *J*=8.1Hz, C-2-H), 7.58 (d, 2H, *J*=9.6Hz, Ar-H), 7.40 (d, 2H, *J*=9.0Hz, Ar-H),7-24-7.17(m,4H, Ar-H),6.87 (s,1H, C-6a-H). Mass spectrum, m/z (%):395 (1.9) M^+,330(12.8), 133 (100).

General procedure Synthesis of 3-arylquinazolin-2,4(1H,3H)-diones 14–21

A solution of 5-haloisatoicanhydride or

N-methylisatoicanhydride1a-c (1mmol) with different amines3a-c (1mmol) in ethanol (20ml) in presence of few drops of acetic acidwere subjected to ultrasound irradiation at 80°C for suitable time until no starting materials were detectable in TLC. The products were then evaporated and recrystallized from aqueous ethanol. The synthesized 3-arylquinazolin-2,4(1H,3H)-diones 14-21 with their physical data are listed below:

3-(2-Methoxybenzyl)-1-methylquinazolin-2,4(1H,3H)-dione (14)

Yield:84%, mp:95-97°C, IR (KBr, cm^{-1}) 1629 and1584 (C=O). ^{1}H NMR (400Hz, $CDCl_3$); δ 7.32 (d, 1H, =7.2Hz,C-8-H), 7.30 (d,1H, *J*=8.8Hz,C-5-H), 7.27 (d,1H, *J*=7.6Hz,C-7-H), 6.94 (d,1H, *J*= 8.4Hz,C-6-H), 6.90 (d,1H, *J*=5.2Hz,Ar-H), 6.89 (d, 1H, *J*=8.0Hz,Ar-H), 6.64 (d, 1H, *J*=8.1Hz,Ar-H), 6.54 (dd, 1H, *J*=5.4Hz,Ar-H), 4.51 (d, 2H, *J*=5.8Hz,CH_2), 3.86 (s, 3H, CH_3), 2.84 (s, 3H,CH_3).^{13}C NMR (400Hz, $CDCl_3$); δ 39.6, 39.6, 55.4, 110.4, 111.5, 114.40, 115.3, 120.7,124.1 127.2, 128.9, 129.8, 130.5, 132.7, 150.5, 157.6, 169.5. Mass spectrum, m/z (%):296(1.1) M+,269(22.2), 91 (67).

1-Methyl-3-(1-phenylpropyl)quinazolin-2,4(1H,3H)-dione (15)

Yield: 82%, mp: 106-108°C, IR (KBr, cm^{-1}) 1626 and 1577 (C=O). ^{1}H NMR (400Hz, $CDCl_3$); δ 7.54 (d, 1H, C-8-H), 7.42(d, 1H, C-5-H), 7.40(d, 1H, C-7-H), 7.30 (d,1H, C-6-H), 7.26 (d, 2H, Ar-H), 6.66 (d, 2H, Ar-H), 6.58 (m, 1H, Ar-H), 4.8 (m,1H, CH), 2.82 (s,3H, CH_3), 1.94 (q,2H, *J* =7.8Hz, CH_2), 0.97 (t, 3H, *J* =7.2Hz, CH_3). ^{13}C NMR (400Hz, $CDCl_3$); δ 10.8, 23.8, 30.9, 55.1, 111.1, 114.3, 115.0,117.1, 118.9, 126.5, 127.0, 127.34, 128.7,130.3, 132.9, 142.4, 150.74, 154.8. Mass spectrum, m/z (%):294(0.4) M+,266(10.2), 237 (13.5) 133 (46.6).

6-Bromo-3-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (16)

Yield: 90%, mp: 140-142°C, IR (KBr, cm^{-1}); 1664 and 1615 (C=O) and 3305 (NH). ^{1}H NMR (300Hz, DMSO-d_6); δ 8.51 (s, 1H, C-5-H), 7.92(d, 1H, C-8-H), 7.67 (d,1H, C-7-H), 7.24 (d, 2H, *J*= 7.2Hz, Ar-H), 6.89 (d, 2H,J=7.4Hz, Ar-H), 6.5 (s,1H, NH), 4.33 (s, 2H, CH_2), 3.72 (s, 3H, CH_3). Mass spectrum, m/z (%):361 (4.73) M^++1, 360 (4.81) M^+,199(3.6), 121 (100).

6-Bromo-3-(2-methoxybenzyl)quinazolin-2,4(1H,3H)-dione (17)

Yield: 89%, mp: 118-120 °C, IR (KBr, cm^{-1}),1626 and1579 (C=O), 3310 (NH) and 3466 (OH). Mass spectrum, m/z (%):361(0.34) M^++1, 360 (0.35) M^+,303(30.4), 134 (100).

6-Chloro-3-(4-methoxybenzyl)quinazolin-2,4(1H,3H)-dione (18)

Yield: 89%, mp: 101-103°C, IR (KBr, cm^{-1}), 1624 and 1580, (C=O), 3288 (NH) and 3457 (OH).^{1}H NMR (300Hz, DMSO-d_6); δ 8.8 (s,1H, C-5-H), 7.58 (d,1H, *J*=8.0Hz, C-8-H), 7.24 (dd, 1H, *J*=8.4Hz, C-7-H), 6.89 (d, 2H, *J*=8.7Hz, Ar-H), 6.73 (d, 2H, *J*=9Hz, Ar-H), 6.5 (s,1H, NH), 4.34 (s, 2H, CH_2), 3.72 (s, 3H, CH_3).Mass spectrum, m/z (= %):318 (0.22) M^++2,316(0.57) M^+,288(20.2), 134 (52.5).

6-Chloro-3-(2-methoxybenzyl)quinazolin-2,4(1H,3H)-dione (19):

Yield: 86%, mp: 143-145°C, IR (KBr, cm^{-1}),1624 and 1580, (C=O), 3288 (NH), 3457 (OH). ^{1}H NMR (300Hz, DMSO-d_6); δ 8.8 (s,1H, C-5-H), 7.22(d,1H, C-8-H), 7.15 (d,1H, C-7-H), 6.99-6.71 (m, 4H, Ar-H), 6.5 (s,1H, NH), 4.33 (s, 2H, CH_2), 3.80 (s, 3H, CH_3).Mass spectrum, m/z (%):318 (0.29) M^++2, 316(0.62) M^+,301(4.4), 285 (6.7).

6-Chloro-3-(1-phenylpropyl)quinazolin-2,4(1H,3H)-dione (20):

Yield: 82%, mp: 120-122 °C, IR (KBr, cm^{-1}), 1633 and 1583 (C=O), 3288 (NH) and 3453 (OH). ^{1}H NMR (300Hz, DMSO-d_6); δ 8.6 (s,1H, C-5-H), 7.66 (d,1H, C-8-H),7.35(d,1H, C_7-H), 7.29(d,1H, Ar-H), 6.82(d, 2H, Ar-H), 6.68 (m, 1H, Ar-H), 6.5 (s,1H, NH), 4.26 (m, 1H, CH), 1.32 (q, 2H, *J*=7.5Hz, CH_2), 0.91 (t, 3H, *J*=7.2Hz, CH_3). Mass spectrum, m/z (%):316 (0.08) M^++2, 314(0.23) M^+,168(21.8), 153 (26.7),106 (100).

6-Bromo-3-(1-phenylpropyl)quinazolin-2,4(1H,3H)-dione (21):

Yield: 82%, mp: 98-100°C, Mass spectrum, m/z (%):360 (0.28) M^++1, 359(0.34) M^+,343(14.1), 211(14.7),106 (90.8).

Biological activity methodology:

- In vitro screening of inhibition of recombinant PDE7A1 enzyme

The synthesized compounds were tested for enzyme inhibitory activity compared to BRL50481 using fluorescence polarization PDE7A1 Assay Kit (Catalog no. 60370; BPS. Bioscience). Fluorescently labeled c-AMP was incubated with test compounds at different dilutions in 96-well tray together with recombinant PDE7A1 enzyme for 1h. the binding agent was added the produced change in fluorescent polarization was measured using microtiter-plate reader capable of

excitation at wavelengths ranging from 475-495 nm and detection of emitted light ranging from 518-538 nm. Blank value was subtracted from all other values. The inhibitory activity of tested compounds was determined as half maximal inhibitory concentration IC50 in μM[47, 48].

Molecular docking methodology

Molecular modeling studies were performed with MOE (Molecular Operation Environments) 2007.09software chemical computing group release. Geometric optimization for 3-D compounds was performed using Hyperchem release 8.0.7. hypercube Inc. The methodology used for docking was in accordance with the literature[49, 50].

Results and Discussion

Chemistry

Synthesis of 3-substituted 6-aryldihyd - roisoindolo[2,1-a]quinazoline-5,11-diones4–13

Kumar et. al.[51] reported the multicomponent reaction of isatoic anhydride and 2-formylbenzoic acid with *p*-toluidine using ethanol as solvent in presence of montomorillonite K10. The reaction is reported to be acid-catalyzed cyclization mechanism. The reaction was also reported to be catalyzed by acetic acid, the reaction takes place in three consecutive steps; the first step, would be a condensation reaction of the amine with the isatoic anhydride followed by loss of carbon dioxide molecule this step is catalyzed by the presence of acid like acetic acid but not any other stronger acids such as triflouro acetic acid. The next step involves nucleophilic substitution of the free amino group on the carbonyl group of 2- formaylbenzoic acid then followed by another condensation reaction to afford the dihydoisoindoloquinazolinone[52].

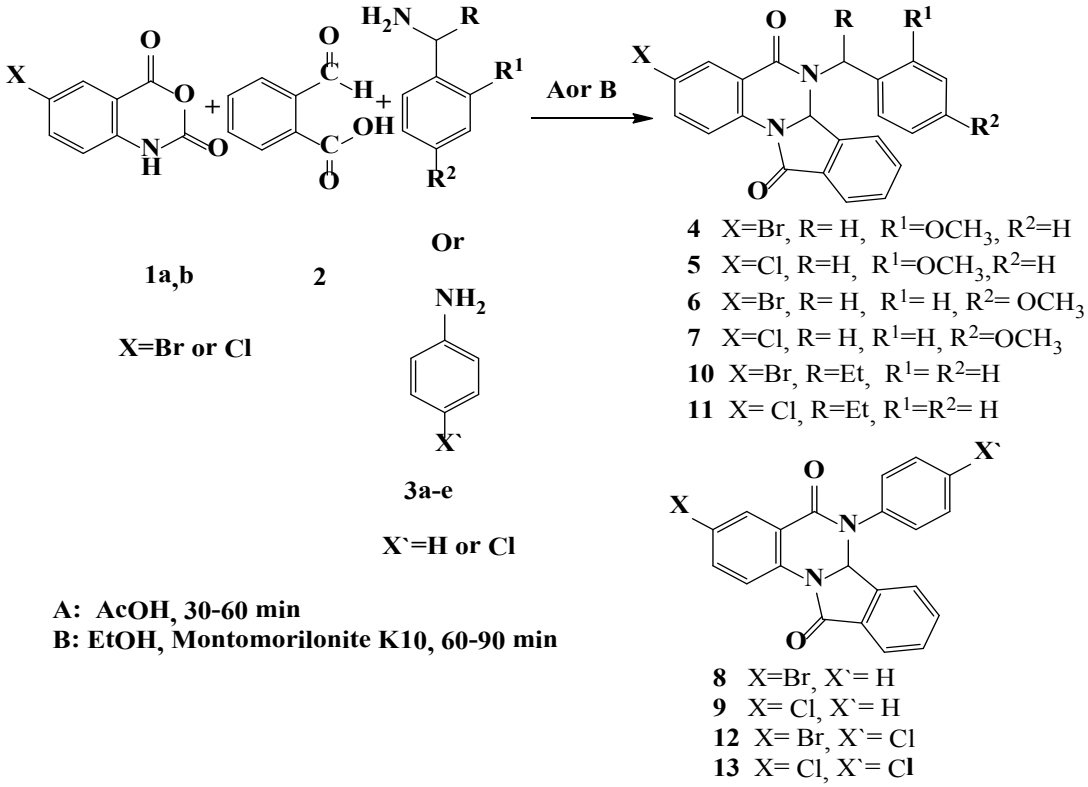
Ultrasoundirradiation is reported to be effective for cyclization reactions so, in the present investigation, ultrasound was used to assist the multicomponent reaction of 5-haloisatoic anhydrides 1a, b, 2-formylbenzoic acid (2) and different amines 3a-e, in two different procedures; Method A; involved use of ethanolin presence of acidic catalyst montomorillonite K10. Method B; involves use of acetic acid as solvent and to catalyze the reaction.Both method A and B were performed under ultrasound irradiation at 80 ^{o}C and were monitored with TLC until one isolable product was detected. Both methods gave the desired products in comparable yields. Method B was the method of choice where it afforded the desired products at comparable yields 86-97% but in shorter time range 30-60 min.

Scheme 1 shows the synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a]quinazolin-5,11-diones **4-13. Table 1** shows one-pot synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a] quinazolin-5,11-diones **4-13** under ultrasound irradiation. Structures of the products were confirmed by mass spectrometry, IR which showed the disappearance of characteristic spike of amino group at 3300 cm^{-1} and showed two characteristic carbonyl peaks at 1680-1720 cm^{-1}. ^{1}H NMR showed a singlet at 6.8 ppm of one proton at C-2 of the quinazoline ring. That carbon showed a characteristic signal at 71 ppm in ^{13}C NMR.

- Synthesis of 3-arylquinazolin-2,4(1H,3H)-diones14–21

The synthesis of quinazolin-2,4(1H,3H)-dione derivatives is reported to proceed through the acetic acid-catalyzed reaction of isatoic anhydride with different amines using ethanol as solvent[53]. In the present investigation, 3-arylquinazolin-2,4(1H,3H)-diones 14–21 were prepared by two methods. Method A; involved the use of ultrasound irradiation at 80 ^{o}C, to assist the reaction of substituted isatoic anhydrides 1a-c with different amines 3a-c in ethanol in presence of few drops of acetic acid. Method B; involved acetic acid-catalyzed reaction of substituted isatoic anhydrides 1a-c with different amines 3a-c in refluxing ethanol. Both methods were monitored by TLC until only one isolable product was obtained. Ultrasound method proved to be superior in both yields and reaction rates. Where the desired products were obtained at yields of 82-92% in time range of 25-45 min. Method B on the other hand, afforded the desired products in time range of 8-12 hours in comparable yields. Table 2 shows the beneficial effect of ultrasound assisted synthesis of 3-arylquinazolin-2,4(1H,3H)-diones 14-21 on reaction times and yields. scheme 2 shows the synthesis of 3-arylquinazolin-2,4(1H,3H)-diones14-21. The elemental analysis and spectral data of the products were compatible with the designed quinazolindione derivatives. The IR showed two characteristic absorption bands of carbonyl in the range 1600-1780 cm^{-1}. The free NH of compounds 16-21 showed stretching peaks at over 3200 cm^{-1}. Stretching peaks of OH appeared at 3400 cm-1 confirming the keto-enol tautomirism. The ^{1}HNMR, showed a peak around 6.5 ppm corresponding to proton on 1- position nitrogen as in compounds 16-21. The proton was

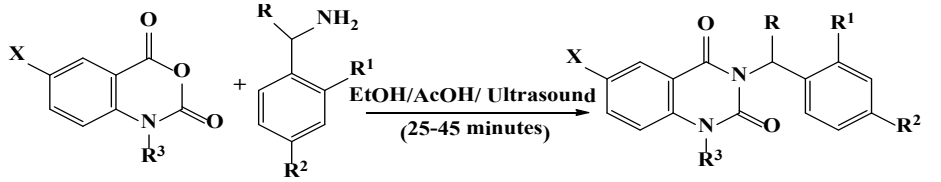
exchangeable with D_2O. A distinct sharp peak around 3.6 ppm corresponding to methoxy protons appeared in compounds. Where, compounds 15, 20 and 21 with phenyl propyl at 3- position showed three characteristic up field-peaks; a triplet at 4.33 ppm corresponding to one proton, a multiplet at 1.3 ppm corresponding to 2 protons and a triplet at 0.9 corresponding to three protons. Compounds 14 and 15 showed a sharp peak up-field at 2.82 corresponding to three protons. In ^{13}CNMR the two characteristic carbonyl carbons appeared down-field at over 150 ppm.



Scheme 1. Synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a] quinazolin-5,11-dione (4-13).

TABLE 1. One-pot synthesis of 3-substituted 6-aryldihydroisoindolo[2,1-a] quinazolin-5,11-diones 4-13 under ultrasound irradiation:

	Ultrasound irradiation			
	Method A		Method B	
	Ethanol/ Montomorillonite K10		Acetic Acid	
Product	Yield%	Time/ (min)	Yield%	Time/ (min)
4	83	90	87	60
5	86	90	89	60
6	93	60	95	45
7	93	60	95	45
8	94	60	94	30
9	94	60	95	30
10	83	90	86	60
11	85	90	88	60
12	92	60	97	30
13	93	60	95	30



1 (a-c) 3(a-c)

14 X=H, R= H, R^1= OCH_3, R^2=H, R^3= CH_3
15 X= H, R=Et, R^1=R^2=H, R^3= CH_3
16 X=Br, R= H, R^1= H, R^2= OCH_3, R^3= H
17 X=Br, R= H, R^1= OCH_3, R^2= H, R^3= H
18 X=Cl, R= H, R^1= H, R^2= OCH_3, R^3= H
19 X=Cl, R= H, R^1= OCH_3, R^2= H, R^3= H
20 X=Cl, R=Et, R^1=R^2=H, R^3= H
21 X=Br, R=Et, R^1=R^2=H, R^3= H

Scheme 2. Synthesis of 3-arylquinazolin-2,4(1H,3H)-diones 14–21.

TABLE 2. Beneficial effect of ultrasound-assisted synthesis of 3-arylquinazolin-2,4(1*H*,3*H*)-diones 14-21 on reaction times and yields.

	Method A		Method B	
	Ultrasound Ethanol/ Acetic acid		Reflux Ethanol/Acetic acid	
Product	Yield%	Time/ (min.)	Yield%	Time/ (hr.)
14	87	45	85	12
15	82	45	80	12
16	92	25	90	8
17	88	30	85	12
18	90	25	88	8
19	87	30	83	12
20	88	30	83	12
21	89	30	85	12

Biological activity

Invitro screening of inhibition of recombinant PDE7A1 enzyme

Seventeen compounds were subjected to in vitro PDE7A1 inhibitory assay kit (catalog no. 60370, BPS Bioscience Inc., San Diego, CA, USA) The half-maximal inhibitor concentrations (IC50 μM) were determined and compared to BRL50481(IC50= 0.072 μM) Five compounds 6, 9, 12,17 and 18 showed IC50 of 0.005, 0.0073, 0.004, 0.007 and 0.008 μM respectively indicating high inhibitory activity for the enzyme. Table 3 shows Phosphodiesterase 7A half-maximal inhibitor concentrations (IC50 μM) for tested compounds against recombinant PDE7 enzyme compared to reference drugBRL5048. The highest of which was compound 12 where the heterocyclic ring system was a fused quinazoline with bromo substitution at 6- position and phenyl ring attached to 3-position of the ring system directly with no linker and bearing a chloro substitution at the para position. Compound **6** showed high inhibitory activity as well, having a fused quinazoline ring system bromo substituted at the same position. The phenyl ring on the other hand was attached to 3- position through a methyl linker and having methoxy group at the para position. Compound **9** showed good inhibitory activity its ring system is also a fused dihydroisoindoloquinazoline that bears a chloro substitution on position 6 and carrying an unsubstituted phenyl ring directly attached to 3- position without a linker. Compound **17** on the other hand, had a quinazolinedione ring system with a bromo substitution at position 6 and showed moderate inhibitory activity. The ring system was attached through a methyl linker to a phenyl ring with ortho methoxy substitution. Compound **15** had a quinaolinedione ring system substituted at its 6 position with chlorine and substituted at 3-position with para methoxy substituted phenyl ring through a methyl linker as well. The least inhibitory activity was for compound **11** with fused ring system substituted at position 6 with chlorine and attached with its 3- position to an unsubstituted phenyl ring through α-ethyl methyl linker.

TABLE 3. Phosphodiesterase 7A half-maximal inhibitor concentrations (IC50 µM) for tested compounds against recombinant PDE7 enzyme compared to BRL5048.

Compound	PDE7A1 (IC50 µM) IC50 µM
4	0.02
5	0.03
6	4.8×10^{-3}
7	0.02
8	0.34
9	7.3×10^{-3}
10	0.02
11	0.14
12	3.9×10^{-3}
13	0.04
14	0.01
15	0.07
16	0.09
17	6.9×10^{-3}
18	8.1×10^{-3}
19	0.06
20	0.03
BRL50481	0.07

Molecular docking

Even though all PDEs have different architecture, they all share two key elements that enables their binding: stacking against a particular phenylalanine residue and hydrogen bonding with defined glutamine residue. The catalytic domain of PDE7A1 is represented by residues (130-482) which has 17 α-helices. It shows two divalent metals zinc and magnesium. Study of the mode of interaction of PDE7A1 in complex with the non-selective inhibitor (3-isobutyl-1-methylxanthine) IBMX available on RCSB Protein Data Bank (PDB entry 1ZKL) [54]showed stacking against Phe416, hydrogen bond interaction with Glu413. It also revealed van der Waals interaction with Tyr211, Val330, Phe384, in addition hydrophobic interaction with Phe384, Ile412, and Phe416. Figure 1 shows IBMX at the binding site of enzyme PDE7A1. On the light of these findings docking study was performed for all the synthesized compound in order to inspect the existence of two main entries hydrogen bonding with Glu413 and stacking against Phe416. The binding mode and binding affinity were compared with that of reference compound BRL50481. All the compounds were docked using the MOE 2007.09 program. Enzyme PDE7A1 was obtained from the RCSB Protein Data Bank (PDB entry 1zkl). BRL50481showed stacking against Phe416 and hydrogen bond with Glu413. Figure 2 shows BRL50481 at enzyme PDE7A1 binding site. The energy score for binding affinity with the enzyme was -8.76K.cal./mol. As for the new synthesized compounds,eight of them fitted perfectly in the binding pocket, compounds 5, 6, 7, 9, 12,15,16 and 19 were able to form hydrogen bonding with Glu413, stacking against Phe416, as well as hydrophobic interactions with different amino acids in the binding site they showed higher binding affinity then the reference drug. Table 4 shows Compounds with their binding affinity (kcal/mol) to PDE7A1 enzyme at its binding site compared to reference compound BRL50481. Figures 3,4, 5, 6, 7, 8, 9 and 10 show compounds 5, 6, 7, 9, 12,15,16 and 19at enzyme PDE7A1 binding site respectively.

TABLE 4. Compounds with their binding affinity (kcal/mol) to PDE7A1 enzyme at its binding site compared to reference compound BRL50481.

Compound	Binding affinity(kcal/mol)
12	-11.90
6	-11.17
9	-11.07
7	-10.40
5	-10.35
19	-9.88
15	-9.62
16	-9.18
BRL50481	-8.76

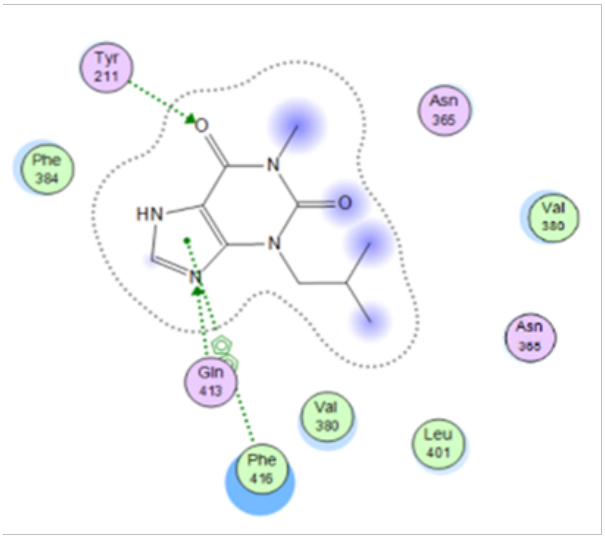


Fig. 1. Binding mode of IBMX at enzyme PDE7A1 enzyme binding site.

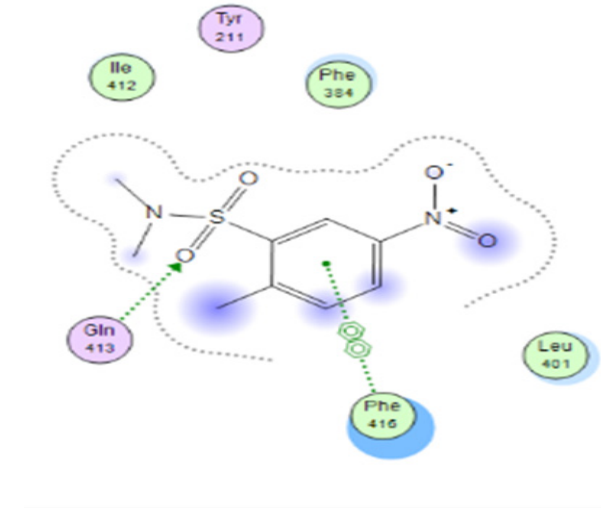


Fig. 2. Binding mode of BRL50481 at enzyme PDE7A1 enzyme binding site.

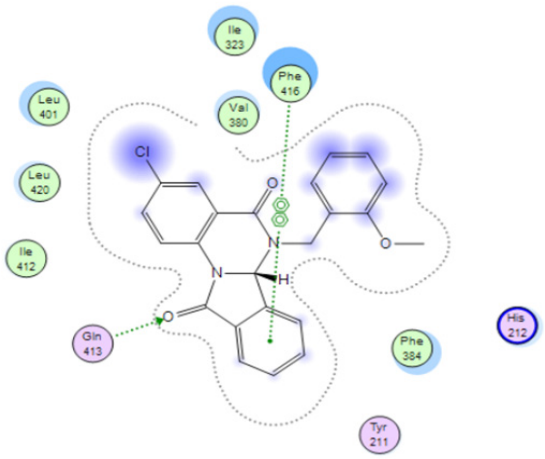


Fig. 3. Binding mode of Compound 5 at enzyme PDE7A1 enzyme binding site.

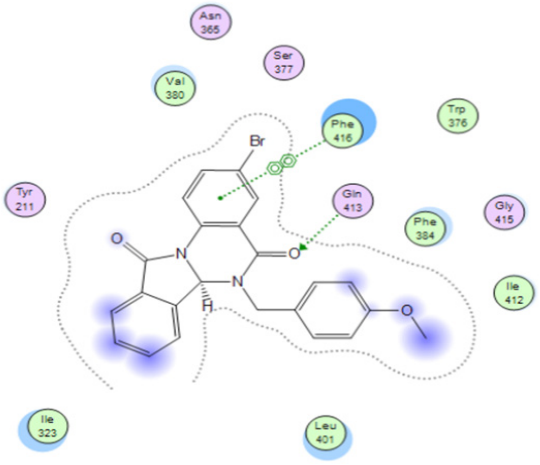


Fig. 4. Binding mode of Compound 6 at enzyme PDE7A1 enzyme binding site .

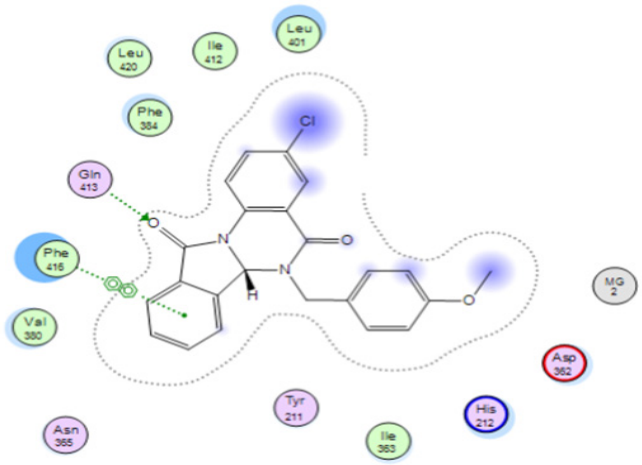


Fig. 5. Binding mode of Compound 7 at enzyme PDE7A1 enzyme binding site.

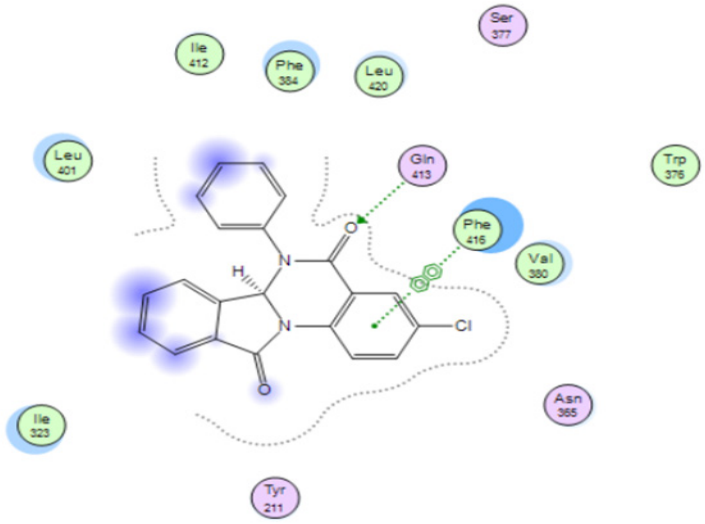


Fig. 6. Binding mode of Compound 9 at enzyme PDE7A1 enzyme binding site.

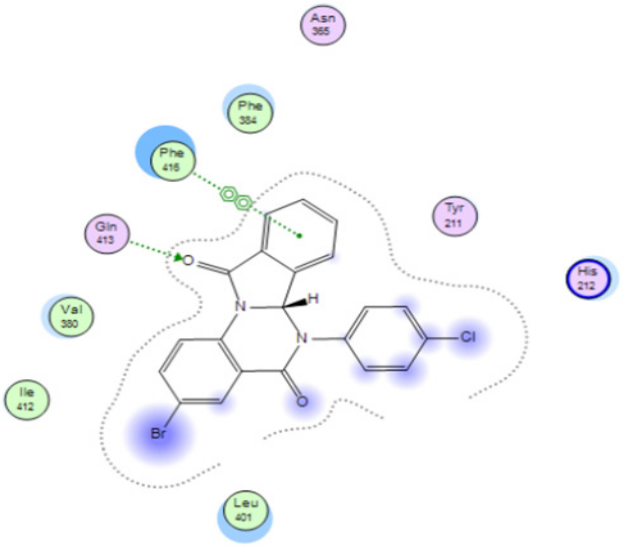


Fig. 7. Binding mode of Compound 12 at enzyme PDE7A1 enzyme binding site

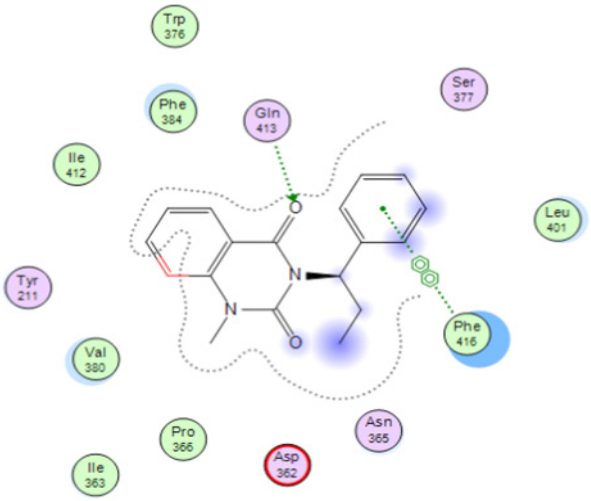


Fig. 8. Binding mode of Compound 15 at enzyme PDE7A1 enzyme binding site.

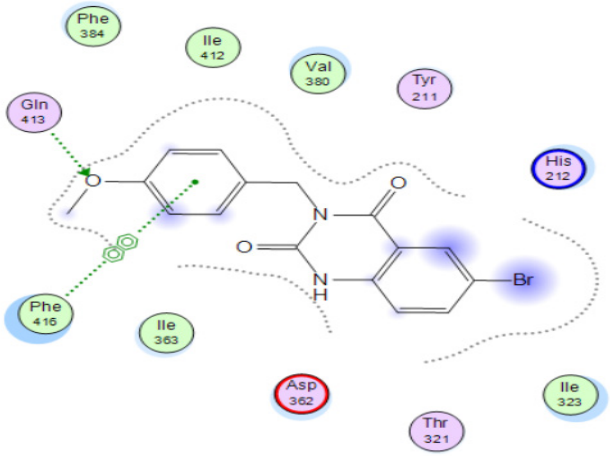


Fig. 9. Binding mode of Compound 16 at enzyme PDE7A1 enzyme binding site.

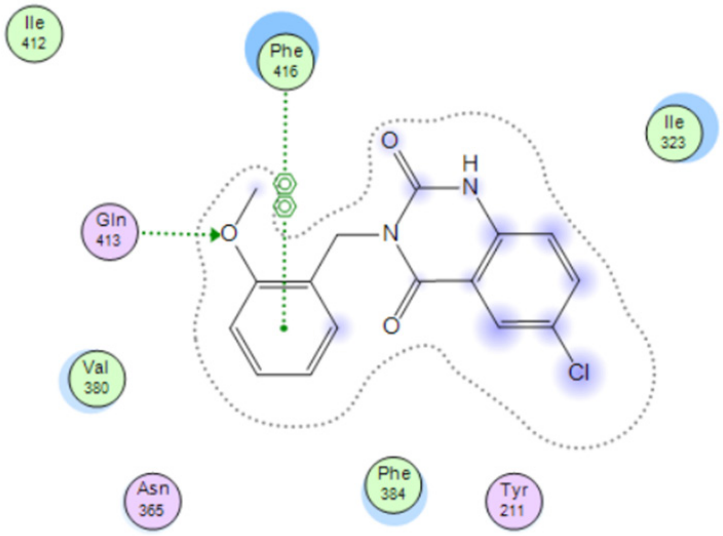


Fig. 10. Binding mode of Compound 19 at enzyme PDE7A1 enzyme binding site.

Conclusion

Seventeen novel quinazolinones derivatives were synthesized and screened for their PDE7A1 enzyme inhibitory activity. All showed enzyme inhibitory activity at micro-molar level. Five compounds showed high potency compared to reference drug. Molecular docking was used to study the binding mode of all the synthesized compounds at the enzyme PDE7A1 binding site. There is a strong relation between the molecular modeling results and the in vitro enzyme inhibitory assay for the compounds. Compounds 6,9 and 12 showed highest inhibitory activity of the enzyme and high binding affinity in the molecular docking and can be subjects for further evaluation as selective PDE7A1 and anti-inflammatory agents.

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استخدام الموجات فوق الصوتية لتحضير مركبات الكينازولينونات والكينوزولين دايونات ودراسةالفحص البيولوجى والالتحام الجزيئي لتلك المركبات كمثبطات لأنزيم فوسفات ثنائى الأستريز 7

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يعتبر انزيم الفوسفوثنائي الاستريز ٧ أحد أهم المستقبلات التى يمكن استهدافها لتصميم مضادات التهابات ذات فعالية عالية مع وجود تاثيرات جانبية محدودة. الكينازولينات تعتبر من اهم الوحدات البنائية فى الكيمياء الطبية نظرا للمدى الواسع من الفعالية البايولوجية الذى تقدمه. العديد من الكينازولينات اثبتت فعالية كمثبطات لانزيم انزيم الفوسفوثنائي الاستريز٧ وكمضادات محتملة للالتهابات وخاصة المزمنة منها كما اثبتت فعالية ضد أمراض المناعة الذاتية. تعتبر الموجات الفوق صوتية طريقة بيئية ومناسبة لتشييد عدد كبير من الحلقات الغير متجانسة وتعتبر اكثر فعالية بالمقارنة بالكيميائ الكلاسيكية فيما يتعلق بتقليل زمن التفعلات وتحسن الناتج. تم استخدام الموجات الفوق صوتية فى تفاعل الاناء الواحد لتشييد ٣-مستبدل ٦-ارايل- داىهايدرو ايزواندولو[٢و١] كينازولين-٥و١١دايونات. وتشييد ٣- ارايل كينازولين ٢و٤ دايونات. تم تشييد سبعة عشر مركبا جديدا . تم اجراء مسح بايولوجي على المركبات المشيدة كموانع لانزيم الفوسفوثنائي الاستريز ٧ علي مستوي الخلايا ز كم تم اجراء دراسة نمذجة جزيئية لدراسة مدى ارتباط المركبات بالانزيم. خمسة مركبات أظهرت فعالية عالية كمثبطات للانزيم عند تركيزات منخفضة بالمقارنة لادواء المرجعي . كما أظهرت تلك المركبات قدرة على التعرف على الآنزيم فى النمذجة الجزيئيى ونمطا فى الارتباط مشابها للمركب المرجعي.