ORIGINAL ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Design and Synthesis of some Azoles Incorporating Sulphadiazine Derivatives as Protein Tyrosine Phosphatase-1B inhibitors

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Received on: 15.07. 2019

Revised on: 10. 09. 2019

Accepted on: 15. 09. 2019

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Abstract

In an effort to development of new protein tyrosine phosphatase-1B (PTP-1B) inhibitors with good bioavailability and cellular permeability, new series of oxothiazolidine, thiazolidine, oxazolidine, oxothiazolidin, pyrrole, and piperazine, of N-(pyrimidin-2-yl)benzene sulfonamide derivatives were synthesized using sulfadiazine as a starting material. The antidiabetic activity of the sulfadiazine derivatives against PTP-1B was determined using molecular simulation with glide docking. The newly synthesized compounds were characterized by both analytical and spectral data.

Keywords: Oxothiazolidine/ Thiazolidine/Oxazolidine/ Pyrrole/ Piperazine/ / N-(pyrimidin-2-yl) benzenesulfonamide.

1. Introduction

PTP-1B malfunctions are linked to various diseases including, diabetes, obesity and cancer neurological disorders **(Heneberg et al., 2009 & Combs et al., 2010)**. In previous of our study, series of neutral benzene sulfonamide containing compounds were synthesized and evaluated as PTP-1B inhibitors. Among the synthesized compounds, **MSE-13** and **MSE-14** showed the most *in vitro* potent PTP-1B inhibitory activity (IC50 of 0.88 µM and 3.33 µM, respectively (**Fig. 1**) **(Ghareb et al., 2019)**. In continuous of our work to discover potent PTP-1B inhibitors with good bioavailability and cellular permeability**,** new series of oxothiazolidine, thiazolidine; oxazolidine, oxothiazolidin, pyrrole, and piperazine, of N-(pyrimidin-2-yl) benzenesulfonamide was decided to synthesize and the antidiabetic activity against PTP-1B

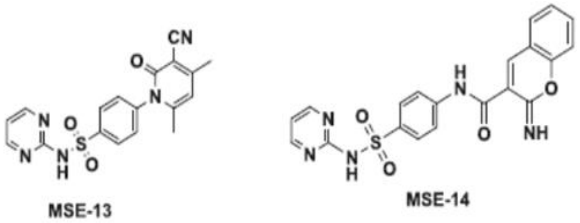


Fig. 1

was determine using molecular simulation with glide docking

2. Results and Discussion

2.1. Chemistry

N-acylation of sulfadiazine, 4-amino-N-(pyrimidine-2-yl) benzene sulfonamide, with 2-chloroacetyl chloride in the presence of triethylamine and DMF afford 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl) acetamide **1 (Khattab et al., 2013).** In this reaction, triethylamine was used to scavenge the released hydrogen chloride during the reaction. The IR spectra showed absorption band of amidic carbonyl (C=O) at 1681 cm^{-1}. In addition, coupling reaction of chloroacetamide **1** with appropriate isothiocyanate or phenyl isocyanate in the presence of pyridine, followed by nucleophilic substitution of chlorine by the sulfur or oxygen atom of isothiocyanate or isocyanate resulted in the formation of thiazolidin, oxazolidin, and oxothiazolidin- of N-(pyrimidin-2yl)benzene sulfonamide derivatives **2,3,4 (Fig. 2) (Moghaddam et al., 2007).**The ^{1}H-NMR spectra of these compounds exhibited a single signal of CH_2 of thiazolidine and oxazolidine rings at 3.51 ppm. Ethyl group of compound **4** exhibited a triplet signal of CH_3 at 1.30 ppm and quadrat signal of CH_2 at 3.20 ppm.

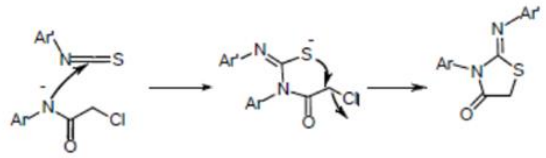


Fig. 2

On another hand, The initial alkylation of chloroacetamide **1** with ethyl cyanoacetate gave dihydropyrrole intermediate followed by intramolecular cyclization which oxidized under the reaction conditions to yield the novel pyrrole derivative **5** (**Fig.3**) **(Farag et al., 2012)**. The IR spectra of this compound exhibited nitrile band (C≡N) at 2194 cm^{-1} as well as two bands at 1662 and 1693 cm^{-1} duo to carbonyl (C=O). When chloroacetamide **1** was heated under reflux with N-substituted piperazine in acetonitrile led to formation of substituted piperazin-1-yl)-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **6-7 (Kumar et al., 2012)**. The ^{1}H-NMR characterized by multiplet signal at δ_H 2.16-3.60 for $(CH_2)_4$ of piperazine ring. On another hand, cyclization of chloroacetamide **1** with ethyl acetoacetate in dimethylformamide and pyridine led to 4-(3-acetyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(pyrimidin-2yl)benzene sulfonamide **8 (Farag et al., 2012).** IR-spectra this compound exhibited characteristic absorption bands for carbonyl group at 1712 cm^{-1}. In addition, chloroacetamide **1** was reacted with ammonium thiocyanate to give 2 thiocyanatoacetamide intermediate which cyclized to 2-imino-4-oxothiazolidine **9 (Fig 3) (Farag et al., 2012)**. The IR spectra of this compound showed two bands at 3194-3271 cm−1 due to NH groups.

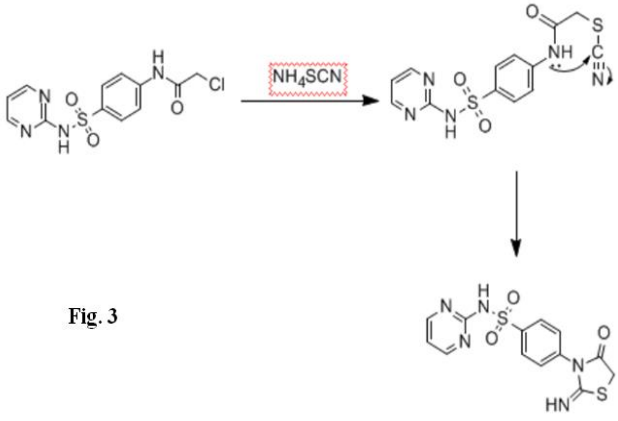


Fig. 3

2.2. Molecular docking

Nowadays molecular modeling simulation becomes a powerful approach for predicting the drug receptor interaction, a benefit which streamlines drug design, discovery, and development. In the current study, the antidiabetic activity of the sulfadiazine derivatives against PTP1B was determined using molecular simulation with glide docking. The crystal structure of PTP1B has been found to compose of a single catalytic domain and some functional loops which regulate the biological dephosphorylation of the protein. The catalytic domain, P-loop, lies between amino acids residue of 214 to 221. Cys 215 is the key amino acid that function the catalytic activity. there are other binding sites besides the P-loop including, the substrate recognition loop, P-Tyr loop, (Tyr46, Val49 and Lys120), Q-loop (Gln262), the WPD loop (Thr177 to Pro185), and the secondary binding site, B-site, (TYR20,ARG24, HIS25, ALA27, PHE52, ARG254, MET258, GLY259). CYS215, ARG221, ASP181, and GLN262 are the key residues for the catalysis (**Fig. 4**) **(Barford et al., 1995 & Pannifer et al., 1998).** In our previous study, it was found that the inhibitors binding solely to active site lack the desired selectivity over other PTPs. Therefore, in this study, the sulfadiazine derivatives were designed to target other sites rather than the catalytic domain. B-site is a secondary binding site adjacent to the P-loop, which is lined by non-conservative and electronically neutral residue. Targeting this site thus might be a practical strategy to achieve the desired selectivity and biological activity. In the current study, molecular modeling simulation showed that interactions of sulfadiazine and PTP1B were dominated by the hydrogen bonding, hydrophobic and electrostatic interactions. GLN262 in Q-loop, ARG47 and ASP48 in P-Tyr loop, ARG24, ARG254 in B-site, and ALA217 were the main amino acids involved in hydrogen bonding. While ALA27, SER28, ASP29, PHE52, CYS32, and MET258 of the B-site were the main residues incorporated in hydrophobic interaction. The aromatic and/or heteroaromatic ring of sulfadiazine derivatives were the main residues involved in the π-π interaction With TYR46 and PHE182 of PTP1B. ASP48, ARG24, and ARG254 are involved in a salt bridge and electrostatic interaction.These types of interaction could provide the desired affinity and high selectivity to PTP1B. Extra precision glide docking of the sulfadiazine derivatives with PTP1B using Schrodinger 10.1 showed a reasonable G score or docking score of -5.03 and a glide Emodel value of -53.78 kcal mol^{-1} for **compound (6)**, compared to dinitro-derivatives (**Fig 5**) that gave a docking score of -5.7 and a glide Emodel value of -61.76 kcal mol^{-1}.

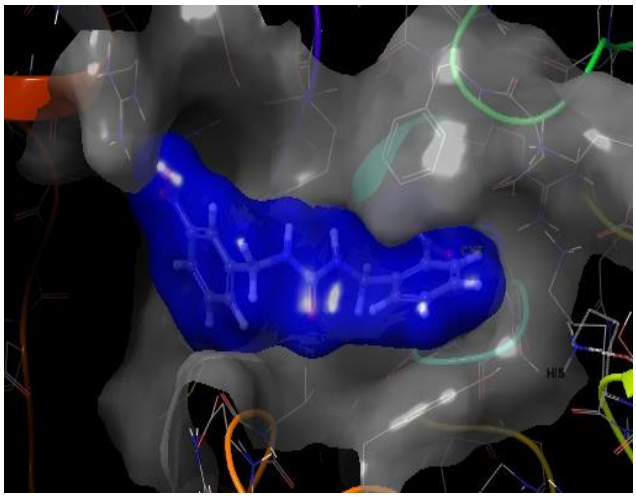
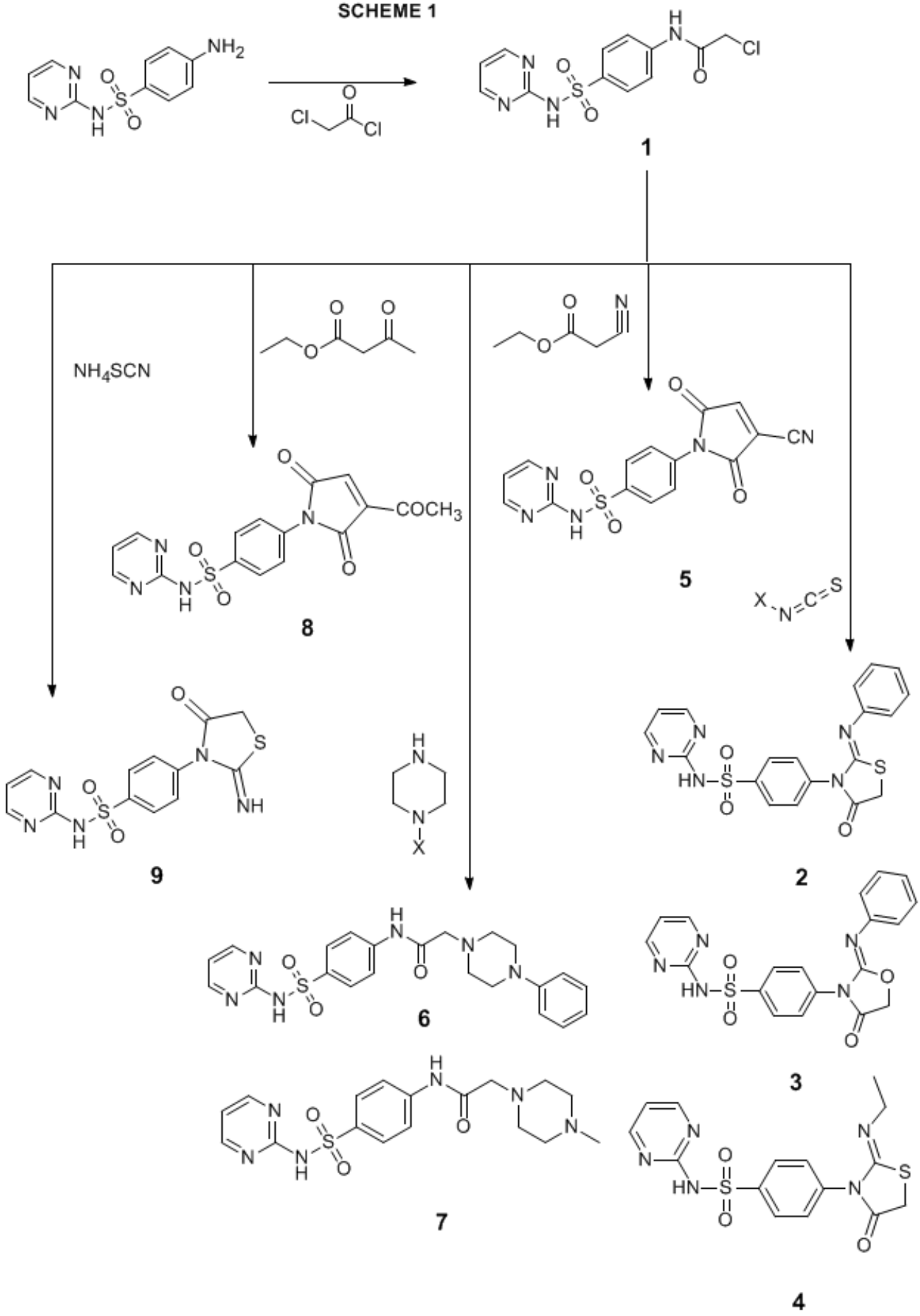


Fig. 4

SCHEME 1



3. Materials and Methods

3.1. Instrument

Melting points were measured in open capillary tubes using Stuart melting point apparatus SMP10 (UK). Infrared (IR) spectra were recorded using KBr discs on a Shimadzu Spectrophotometer (λ_{max} in cm^{-1}). Proton Magnetic Resonance (^{1}H-NMR) and was recorded using the residual solvent signal as an internal standard with a Varian AS 400. Chemical shifts are reported in d values (parts per million, ppm) relative to tetramethylsilane (TMS) as an internal standard. Abbreviations used in NMR analysis are as follows: d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet. Electron impact mass spectra (EI-MS) were recorded on DI Analysis Shimadzu QP-2010 Plus mass spectrometer. Elemental analyses were performed in the Microanalytical center, Cairo University, Egypt. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60_{F254} and visualized with UV light.

3.2. Experimental

3.2.1. Chemistry

2-Chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide 1

In an ice bath, a solution of 4-amino-N-(pyrimidin-2-yl)benzenesulfonamide (0.04 mol, 10 gm) and triethylamine (2 mL) in dry DMF (20 mL) was stirred for 1 hr. 2-chloroacetyl chloride (0.04 mol, 4.48 mL) was then added in portions, and the reaction mixture was stirred for 4 hr. After completion of the reaction monitored by TLC, the mixture was poured, with continuous stirring, on to crushed ice. The solid formed was collected filtration, washed with ethyl acetate, and recrystallized from DMF. M.p.= 228-230˚C, (yield 80%). IR (cm^{-1}): 798(C-Cl), 1165(SO_2 Sym), 1323(SO_2 Asym), 1539(C=N), 1589(C=N), 1681(C=O), 3360(NH), 3425(NH). Mass spectrum: m/z(%): 327(M^++1, 1.03%), 313(2.28%), 299(1.18%), 260(96.73%), 213(14.70%), 185(base peak, 100%), 139(3.41%), 108(13.59%), 92(29.08%), 65(17.82%).

General procedure for the preparation of 2-4

A mixture of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **1** (0.006 mol, 2 gm), pyridine (0.7 mL) and acetonitrile (20 mL) was stirred at room temperature for 30 min; then to this mixture, phenylisothiocyanate or ethylisothiocyanate or phenylisocyanate (0.006 mol) was added dropwise, and the mixture stirred at room temperature for the required time. After completion of reaction monitored by TLC, the solvent was evaporated under reduced pressure to complete dryness and crystallized from DMF.

(Z)-4-(4-oxo-2-(phenylimino)thiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 2

M.p.= 210-212˚C, (yield 40%). IR (cm^{-1}): 570(C-S), 1165(SO_2 Sym), 1334(SO_2 Asym), 1492(C=N), 1543(C=N), 1589(C=N), 1678(C=O), 3379(NH). Mass spectrum: m/z(%): 424(M^+-1, 1.57%), 381(0.82%), 359(44.72%), 327(2.79%), 311(2.48%), 286(4.91%), 260(base peak, 100%), 213(12.37%), 185(68.97%), 133(9.37%), 108(16.54%), 92(45.82%), 65(54.16%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 3.51-3.57 [s, 2H, CH_2-thiazolidinone], 6.61 [d, 1H, H pyrimidine], 7.31–7.99 (m, 9H, Ar-H), 8.28–8.30 (d, 2H, H-

pyrimidine), 8.45 [s, 1H, SO_2NH]. Anal.Calcd. for $C_{19}H_{15}N_5O_3S_2$: C, 53.63; H, 3.55; N, 16.46; S, 15.07. Found: C, 53.29; H, 3.38; N, 16.15; S, 15.11.

(Z)-4-(4-oxo-2-(phenylimino)oxazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 3

M.p.= 200-202˚C, (yield 33%). IR (cm^{-1}): 1165(SO_2 Sym), 1234(C-O-C), 1334(SO_2 Asym), 1543(C=N), 1566(C=N), 1589(C=N), 1678(C=O), 3317(NH). Mass spectrum: m/z(%): 409(M^+, 0.71%), 393(1.08%), 369(1.25%), 339(4.20%), 313(12.80%), 299(4.47%), 285(2.01%), 261(58.18%), 213(8.35%), 185(36.41%), 158(5.57%), 133(9.04%), 108(17.65%), 93(56.83%), 65(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 3.48 [s, 2H, CH_2-oxazolidinone], 6.59 [d, 1H, H-pyrimidine], 6.85-7.35 (m, 9H, AR-H), 7.78-7.80 (d, 2H, H-pyrimidine), 8.85 [s, 1H, SO_2NH]. Anal.Calcd. for $C_{19}H_{15}N_5O_4S$: C, 55.74; H, 3.69; N, 17.11; S, 7.83. Found: C, 55.75; H, 3.67; N, 17.13; S, 7.79.

(Z)-4-(2-(ethylimino)-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 4

M.p.= 220-221˚C, (yield 50%). IR (cm^{-1}): 580(C-S), 1165(SO_2 Sym), 1334(SO_2 Asym), 1496(C=N), 1543(C=N), 1589(C=N), 1678(C=O), 3379(NH). Mass spectrum: m/z(%): 377(M^+, 2%), 350(20%), 305 (23%), 261(69.78%), 213(10.72%), 185(96.33%), 168(8.81%), 140(6.17%), 119(4.90%), 92(63.99%), 77(58.41%), 65(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 1.30 [t, 3H, CH_3], 3.13–3.20[q, 2H, CH_2], 4.60 [s, 2H, CH_2- oxothiazolidine], 7.48 [d, 1H, H-pyrimidine], 7.52–7.71 (m, 4H, Ar-H), 7.78–7.80 (d, 2H, H-pyrimidine), 10.54 [s, 1H, SO_2NH]. Anal.Calcd. for $C_{15}H_{15}N_5O_3S_2$: C, 47.73; H, 4.01; N, 18.55; S, 16.99. Found: C, 47.57; H, 3.92; N, 18.34; S, 16.81.

4-(3-cyano-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 5

A mixture of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **1** (0.006 mol, 2 gm) and ethyl cyanoacetate (0.006 mol, 0.69 mL) in dimethylformamide (50 mL) containing pyridine (0.5 mL) was heated under reflux for 6 h, then left to cool to r.t. The precipitated product was filtered off and recrystallized from DMF. M.p.= 215-217˚C, (yield 53%). IR (cm^{-1}): 1157(SO_2 Sym), 1338(SO_2 Asym), 1535(C=N), 1585(C=N), 1662(C=O), 1693(C=O), 2194(C≡N), 3329(NH). Mass spectrum: m/z(%): 355(M^+, 1.65%), 340(3.20%), 328(1.73%), 306(0.77%), 285(0.94%), 273(3.36%), 227(49.26%), 211(4.46%), 185(8.64%), 171(5.02%), 160(4.89%), 143(7.48%), 126(7.57%), 111(14.98%), 90(23.68%), 71(49.15%), 44(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 6.53 [s, 1H, CH- pyrrole], 6.81-6.85[d, 1H, H-pyrimidine], 7.55 -7.83 (m, 4H, Ar-H), 8.02–8.03 (d, 2H, H-pyrimidine), 8.16 [s, 1H, SO_2NH]. Anal.Calcd. for $C_{15}H_9N_5O_4S$: C, 50.70; H, 2.55; N, 19.71; S, 9.02. Found: C, 50.73; H, 2.55; N, 19.70; S, 9.02.

General procedure for the preparation of 6-7

A solution of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **1** (0.003 mol, 1 gm), in acetonitrile (20 mL) was stirred at room temperature for 1 hr; then to this mixture, N-methylpiperazine or N-phenylpiperazine (0.003

mol) was added, and the mixture stirred at room temperature for 12 hr. After completion of reaction monitored by TLC, the solvent was evaporated under reduced pressure to complete dryness and crystallized from DMF.

2-(4-phenylpiperazin-1-yl)-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide 6

M.p.= 278-280˚C, (yield 44%). IR (cm^{-1}): 1153(SO_2 Sym), 1234(C-N), 1311(SO_2 Asym), 1570(C=N), 1604(C=N), 1678(C=O), 3255(NH), 3360(NH), Mass spectrum: m/z(%): 453(M^++1, 2.24%), 452(M^+, 7.74%), 295(0.77%), 263(2.25%), 213(7.38%), 175(base peak, 100%), 160(8.66%), 132(21.73%), 104(13.96%), 70(22.98%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) 2.16-3.60 (m, 8H, $(CH_2)_4$ piperazine), 4.20 [s, 2H, CH_2], 6.93-6.95[d, 1H, H-pyrimidine], 7.01-7.45 (m, 9H, Ar-H), 7.74-7.76–8.03 (d, 2H, H-pyrimidine), 8.59-8.64 [s, 2H, (SO_2NH, NH acetamide)]. Anal.Calcd. for $C_{22}H_{24}N_6O_3S$: C, 58.39; H, 5.35; N, 18.57; S, 7.09. Found: C, 58.56; H, 5.34; N, 18.64; S, 7.17.

2-(4-methylpiperazin-1-yl)-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide 7

M.p.= 285-287˚C, (yield 52%). IR (cm^{-1}): 1134(SO_2 Sym), 1261-1246(C-N), 1307(SO_2 Asym), 1535(C=N), 1581(C=N), 1697(C=O), 3178(NH), 3248(NH). Mass spectrum: m/z(%): 390(M^+, 0%), 277(0.79%), 263(2.14%), 213(3.79%), 185(62.31%), 170(3.93%), 140(2.92%), 113(56.51%), 92(80.65%), 65(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm)= 1.11(s, 3H, CH_3), 2.20-2.65 (m, 8H, $(CH_2)_4$ piperazine), 3.64 [s, 2H, CH_2], 7.50-7.55[d, 1H, H-pyrimidine], 7.72-7.99 (m, 4H, Ar-H), 8.12-8.15 (d, 2H, H-pyrimidine), 8.41-8.43 [s, 2H, (SO_2NH, NH acetamide)]. Anal.Calcd. for $C_{17}H_{22}N_6O_3S$: C, 52.29; H, 5.68; N, 21.52; S, 8.21. Found: C, 52.51.; H, 5.97; N, 21.28; S, 8.40.

4-(3-Acetyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 8

A mixture of 2-chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **1** (0.006 mol, 2 gm) and ethyl acetoacetate (0.006 mol, 0.79 mL) in dimethylformamide (20 mL) containing pyridine (0.5 mL) was heated under reflux for 4 h. The solvent was evaporated under reduced pressure to complete dryness and crystallized from ethanol. M.p.= 240-242˚C, (yield 56%). IR (cm^{-1}): 1130(SO_2 Sym), 1307(SO_2 Asym), 1600(C=N), 1712(C=O), 1666(C=O), 3354(NH). Mass spectrum: m/z(%): 372(M^+, 1.13%), 358(3.29%), 334(1.37%), 306(1.26%), 283(1.39%), 264(54.20%), 249(20.31%), 234(2.63%), 209(2.14%), 170(16.78%), 124(16.90%), 92(61.79%), 65(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm) = 2.17 (s, 3H, CH_3), 6.83 [s, 1H, CH- pyrrole], 7.03-7.09[d, 1H, H-pyrimidine], 7.20 -7.58 (m, 4H, Ar-H), 7.81-7.83 (d, 2H, H-pyrimidine), 8.24 [s, 1H, SO_2NH]. Anal.Calcd. for $C_{16}H_{12}N_4O_5S$: C, 51.61; H, 3.25; N, 15.05; S, 8.61.Found: C, 51.33; H, 3.49; N, 15.09; S, 8.60.

4-(2-imino-4-oxothiazolidin-3-yl)-N-(pyrimidin-2-yl)benzenesulfonamide 9

2-Chloro-N-(4-(N-pyrimidin-2-ylsulfamoyl) phenyl)acetamide **1** (0.006 mol, 2 gm) and ammonium thiocyanate (0.0062 mol, 0.5 gm) in 50 mL of ethanol (HPLC) was heated under reflux for 10 h, left overnight, and poured into cold

water. The solid product was filtered and crystallized from ethanol. M.p.= 250-252˚C, (yield 67%). IR (cm^{-1}): 690(C-S), 1161(SO_2 Sym), 1334(SO_2 Asym), 1669(C=N), 1677(C=N), 1681(C=O), 3194(NH), 3271(NH). Mass spectrum: m/z(%): 349(M^+, 1.99%), 325(8.70%), 312(58.55%), 289(5.72%), 253(16.05%), 239(11.15%), 211(11%), 196(4.51%), 185(48.32%), 171(20.33%), 157(10.54%), 131(27.34%), 105(37.41%), 92(48.33%), 77(64.53%), 44(base peak, 100%). ^{1}H-NMR (DMSO-*d*6, 400 MHz): δ (ppm)= 3.77 (s, 2H, CH_2 oxothiazolidin), 7.24[d, 1H, H-pyrimidine], 7.28-7.38 (m, 4H, Ar-H), 7.75-7.77 (d, 2H, H-pyrimidine), 8.43-8.45 [s, 2H, (SO_2NH, NH imino)]. Anal.Calcd. for $C_{13}H_{11}N_5O_3S_2$: C, 44.69; H, 3.17; N, 20.04; S, 18.35. Found: C, 44.43; H, 3.35; N, 20.19; S, 18.02.

3.2.2 Molecular Modeling Experiment

In the current research, a molecular modeling study was conducted using the Glide docking function incorporated in the Schrodinger-10.1 molecular modeling program. The X-ray crystal structure of the catalytic domain of PTP1B enzyme in complex with sulfamic acid inhibitor (PDB ID: 2F70 resolution 2.6 Å) was obtained from Protein Data Bank (PDB) **(http://www.rcsb.org/pdb**. The PTP1B-sulfamic acid complex was refined for the Glide docking calculations using the protein preparation wizard applying the OPLS-2005 force field. In the second step, crystallographic water, if present, was removed, and hydrogens were added to the structure corresponding to pH 7.0, most likely positions of hydroxyl and thiol hydrogen atoms, considering the appropriate ionization states for both the basic and acidic amino acid residues of the protein. In the third step, the appropriate charge and protonation state of protein were adjusted by the protein assignment script, then the protein-inhibitor complex was subjected to energy minimization until the average root mean square deviation (RMSD) of the non-hydrogen atoms reached 0.3 Å in order to release the steric clashes using the OPLS-2005 force field (**(Halgren et al., 2004 & Abdelhameed et al., 2016).**

Using ligand preparation wizard, the 3D structures of the sulfadiazine derivatives were constructed and optimized with the build panel in Maestro. The ligand preparation function generates several low energy 3D structures with various ionization states, tautomers, stereochemistries, and ring conformations, for each input molecule. Partial atomic charges were ascribed for sulfadiazine derivatives using the OPLS-2005 force-field, and possible ionization states were generated at a pH of 7. To soften the potential for non-polar parts of the receptor, the van der Waal radii of receptor atoms were scaled by 0.8 with a partial atomic charge of 0.15. A grid box with coordinates X = 10, Y = 10 and Z = 10 was generated at the centroid of the active site. The ligand structures thus obtained were further optimized by energy minimization until it reached RMSD cutoff of 0.01 Å. The properties and the shape and of the active site of PTP1B were characterized using “grid generation panel” in Glide after ensuring that the PTP1B receptor and sulfadiazine molecules were in the correct form (https://isp.ncifcrf.gov/files/isp/uploads/2010/07/lp23_user_manual.pdf

In the final step, the sulfadiazine derivatives were docked within the active site of PTP1B using the optimized protein-ligand geometries. The extra precision (XP) Glide scoring function, which docks ligands flexibly, is applied to rank the docking poses and to assess the protein-ligand binding affinities. Maestro's Pose Viewer utility was utilized to visualize and analyze the key elements of ligand- receptor interaction. The final best-docked structure with the lowest-energy was chosen using a glide score function and selected for further experiments. Sulfamic acid inhibitor was removed from the crystal structure PTP1B receptor then re-docked using the previous-mentioned step to evaluate the accuracy and precision of established docking protocol (**(Halgren et al., 2004& Abdelhameed et al., 2016)**.

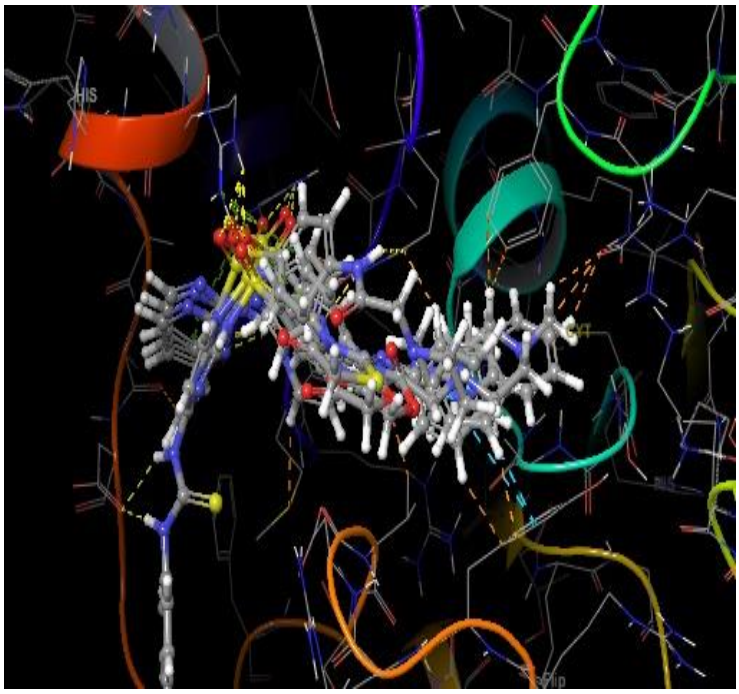
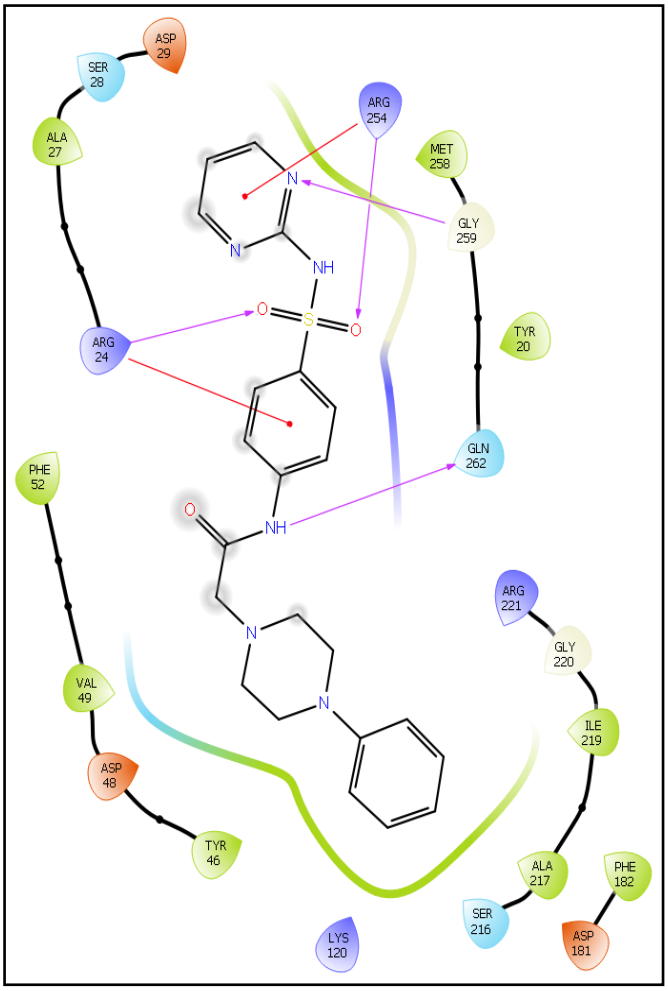
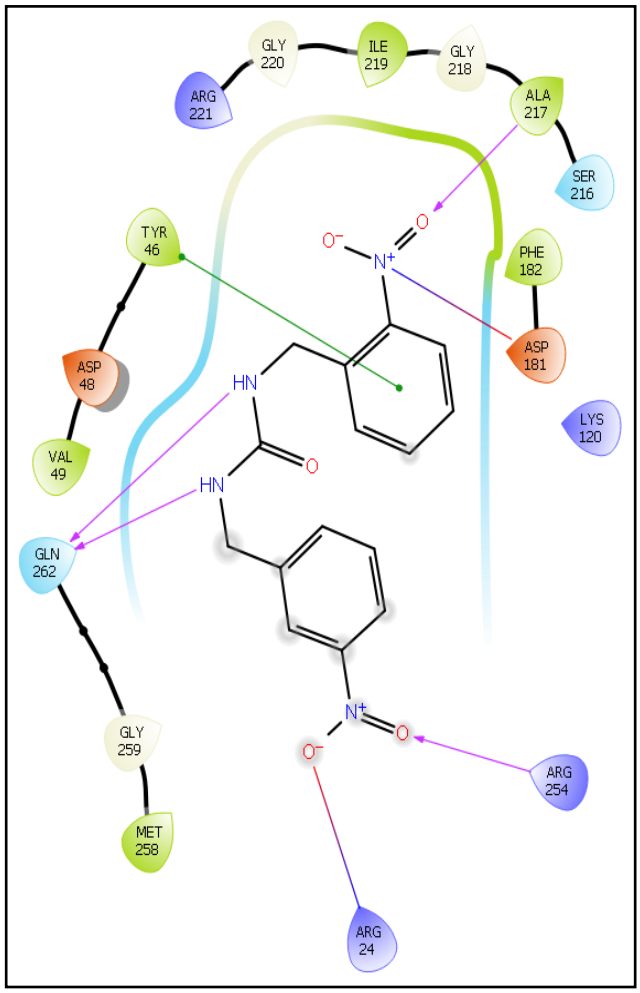


Fig. 5





4. Conclusion

In the last two decades, the inhibition of PTP1B enzyme has emerged as a promising tool for therapeutic monitoring of diabetes mellitus. The main problem limiting the application of PTP-1B inhibitor in diabetes management is the week selectivity of the designed compounds towards PTP1B. In this study, the selectivity of designed compounds over other PTPs was taken in consideration by synthesizing new compounds targeting B-site.

References

Abdelhameed R, Elgawish M S, Mira A. Anti choline esterase activity of ceramides from the Red Sea marine sponge Mycale euplectellioides, RSC Adv. 6: 2016; 20422–20430.

Barford D, Flint A J, Tonks N K. Structural basis for phosphotyrosine peptide recognition by protein tyrosine phosphatase 1B, Science 1995; 268: 1754–1758.

Combs A P, Recent advances in the discovery of competitive protein tyrosine phosphatase 1B inhibitors for the treatment of diabetes, obesity, and cancer. J. Med. Chem. 2010; 53:2333–2344.

Farag A A, Abd-Alrahman S, Ahmed G, Ammar R, and Abbas S. Synthesis of Some Azoles Incorporating a Sulfonamide Moiety as Anticonvulsant Agents. Arch. Pharm. Chem. Life Sci. 2012; 345: 703–712.

Ghareb N, El-Sayed N M, Abdelhameed R, Yamadad K, Elgawishe M S. Toward a treatment of diabesity: Rational design, synthesis and biological evaluation of benzene-sulfonamide derivatives as a new class of PTP-1B inhibitors. Bioorganic Chemistry 2019; 86: 322–338.

Halgren T A, Murphy R B, Friesner R A, Beard H S, Frye L L, Pollard W T and Banks J L. J. Med. Chem. 2004; 47:1750–1759.

Heneberg P. Use of protein tyrosine phosphatase inhibitors as promising targeted therapeutic drugs. Curr. Med. Chem. 2009; 16: 706–733.

Khattab M, Galal Sh, Ragab F, and El Diwani H. Different synthetic routes to 4-(1H benzo[d] imidazol-2-yl)aniline. Res Chem Intermed. 2013; 39:2917–2923.

Kumar A, Vaidya A, Ravichandran V, Kashaw S, and Agrawal R. Recent developments and biological activities of thiazolidinone derivatives: A review. Bioorganic & Medicinal Chemistry 2012; 20: 3378–3395.

Moghaddam F M, Hojabri L J. A Novel Synthesis of Some 2-Imino-4-thiazolidinone Derivatives. J. Heterocyclic Chem. 2007; 44: 35-38.

Pannifer A D, Flint A J, Tonks N K, Barford D. Visualization of the cysteinylphosphate intermediate of a protein-tyrosine phosphatase by x-ray crystallography, J. Biol. Chem. 1998; 273: 10454–10462.