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Synthesis of Medicinally Relevant Phenyl Sulphonylamino Alkanamides and *N*-aryl *P*-toluenesulphonamides

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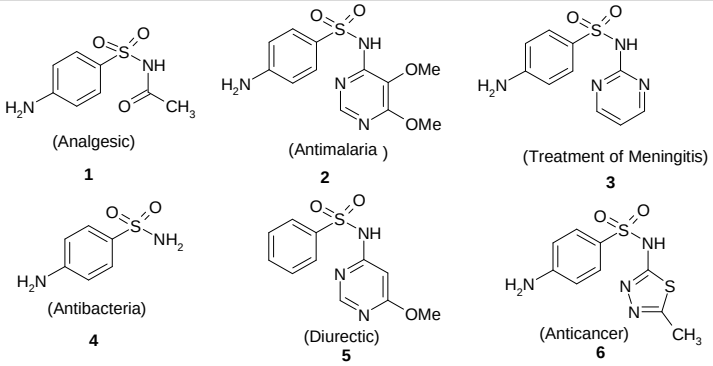
ABSTRACT

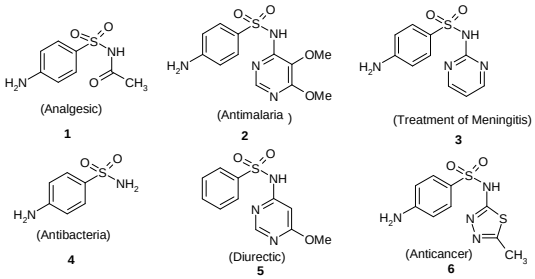
Synthesis of new medicinally important phenylsulphonyl aminoalkanamides and *N*-aryl *p*-toluene sulphonamides is reported. The reaction between benzenesulphonylchloride 7 and valine gave 3-methyl-2-[phenylsulphonyl)amino]butanoic acid 9 which was converted into 2-[acetyl (phenylsulphonyl) amino]-3-methyl butanoic acid 10 by reacting with acetic anhydride in acetic acid. The reaction of the latter with $SOCl_2$ and the former with NH_3 afforded 2-[*N*-acetyl (phenylsulphonyl) amino]-3-methyl butanamide intermediate 11. The palladium-catalyzed reaction of the intermediate with readily available aryl chlorides and bromides afforded a variety of phenyl sulphonylaminoalkanamides 13a-c. In another synthesis, *p*-toluenesulphonylchloride (14) reacted with aqueous ammonia to give 4-methyl benzenesulphonamide 15 which is converted into *N*-(4-hydroxylphenyl)-4-methylbenzene sulphonamide 17a, *N*-(4-formyl phenyl)-4-methyl benzene sulphonamide 17b, *N*-(4-aminophenyl)-4-methyl benzenesulphonamide 17c, 4-methyl-*N*-(2-methylphenyl) benzene sulphonamide 17d, *N*-(4-Methoxyphenyl)-4-methyl benzenesulphonamide 17e in good yields, by reaction with 4-chlorophenol, 4-bromobenzaldehyde , 4-bromoaniline, 2-chlorotoluene and 1-bromo-2-methoxybenzene, respectively. Structures of the synthesized compounds were confirmed by spectroscopic and elemental analytical data.

GRAPHICAL ABSTRACT



Introduction

Sulphonamides constitute a class of organosulphur compounds and are extensively used as anticancer[1], antitumour[2], antiviral[3], antimalarial[4], antidiabetic[5], antihypertensive[6], antituberculosis[7], antiosteoarthiritis[8], anticataract[9], antidiuretics[10], antimigraine[11], antiretroviral[12], and inhibitors of carbonic anhydrase, among others. Some of these sulpha drugs that have performed ‘’healing magic’’ in the world of therapy include Sulphonilamide 1, Sulphadozin 2, Sulphadiazine 3, Sulphanilamide 4, Sulphamonomethoxine 5 and Sulphamethiazole 6.



The target of sulphonamide drugs and the basis of their selectivity is the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway.[13] Nowadays, sulphonamides drugs are occasionally used due to horizontal spread of resistance genes, expressing drug-insensitive variants of target enzymes dihydropteroate synthase.[14] The challenge of the emergence

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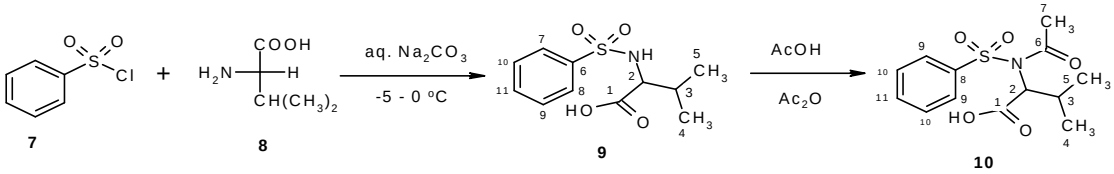
of multidrug resistance micro-organism to clinically used sulphonamide drugs has revived a dedicated search for new antimicrobial drugs to combat rapid spread of harmful microorganisms.[15-20] Sondhi et al synthesized some methanesulphonamides by condensation of 3, 4-diaryl-2-imino-4-thiazolines with methanesulphonyl chloride and found out that they possess anti-inflammatory and anticancer activities.[21] Nassir and his group synthesized *N*-4-methylbenzenesulphonyl N-(4-methylbenzenesulphonyl)-benzimidazol-2-ylmethylthio)benzimidazole in good yields from 2-(benzimidazole-2-yl) methylthio)-benzimidazole.[22] A series of quinazolonyl derivatives of 4-oxothiazolidinyl sulphonamides were synthesized and were found to have remarkable antibacterial activity against *Bacillus subtilis*, *Bacillus cereus*, *Candida albican*.[23] In a six-step synthesis, Chen and co-workers synthesized *N*, *N*-disubstututed 1, 3, 4-thiadiazole-2-sulphonamide derivatives that exhibited certain anti tobacco mosaic virus activity.[24] Also, antimalarial properties of new carboxamides bearing sulphonamide were recently reported.[25] In this article, we described the synthesis of phenylsulphonylaminoalkanamides and *N*-aryl *p*-toluenesulphonamides as medicinally relevant new sulphonamides.

Results And Discussion

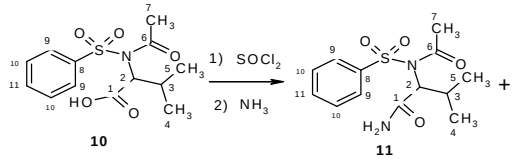
Synthesis

The reaction of benzenesulphonyl chloride 7 with valine 8 under basic condition at room temperature afforded 3-methyl-2-[(phenylsulphonyl)amino]butanoic acid 9 in 75% yields. Compound 9 which is a white crystalline compound, melting at 133-134 ^{o}C, was prepared as described.[26] Heating of a mixture of compound 9 in acetic anhydride and glacial acetic acid under refluxing condition provided 2-[acetyl (phenylsulphonyl)]-3-methylbutanoic acid 10 as a white crystalline solid compound at 85% yield, melting at 102 – 103 ^{o}C. The spectral and analytical data supported the assigned molecular structure of compound 10.

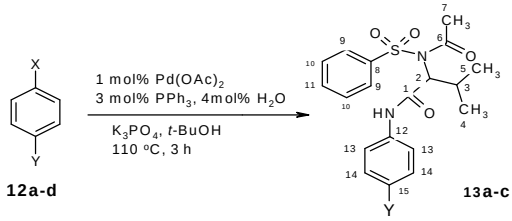


7 8 9 10

The 2-[acetyl (phenylsulphonyl)]-3-methylbutanoic acid 10 in *t*-butanol was converted into 2-[acetyl (phenylsulphonyl)]-3-methylbutanamide 11 by the reaction with excess thionyl chloride under reflux for 3h affording a black crystalline solid, melting at 140 – 142 ^{o}C. The IR



10 11

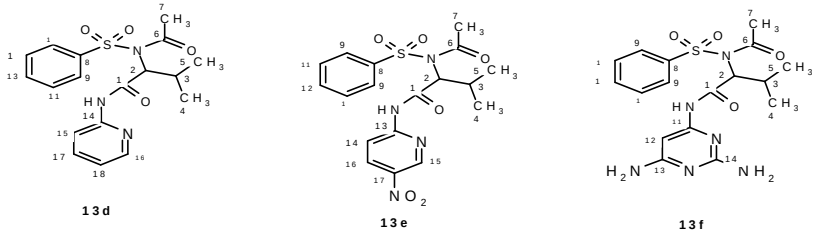


12a-d 13a-c

	12a	12b	12c
X	Cl	Br	Br
Y	OH	NH_2	OCH_3

absorption bands for -NH_2, C=O for amide and S=O appeared at 3262 cm^{-1}, 1708 cm^{-1} and 1382 cm^{-1}, respectively. The proton nuclear magnetic resonance absorption at δ 7.87 – 7.56 (multiplet, 5H) was assigned to aromatic protons, δ 3.60 (singlet, 2H) is due to NH_2 protons, δ 3.08 (singlet, 3H) is due to –CH_3 protons, δ 1.87 – 1.35 (doublet, 1H) is due to C-H protons and δ 0.97 – 0.87 (doublet, 6H) is due to 2CH_3 protons. Other spectral data are in agreement with the molecular structure of compound 11.

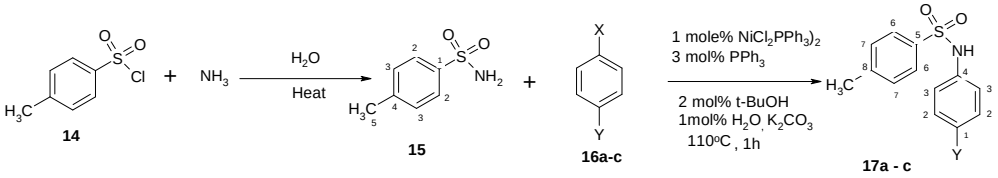
The –NH_2 moiety of the amide group was taken advantage in further conversion of the compound 11 via palladium acetate and triphenylphosphine catalytic cross-coupling afforded mutifuntionalised phenylsulphonylaminobutanamide 13a-13c in good yields. Furthermore, the reaction of compound 11 with 2-chloro-5-nitropyridine and 6-chloro-2, 4-diaminopyrimidine heterocycles provided compounds 13e and 13f respectively after recrystallisation from mixture tertiary butanol and methanol in ratio (1:3).



13d 13e 13f

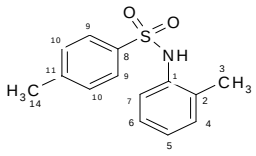
In another development, *p*-toluenesulphonylchloride 14 reacted with ammonium hydroxide in water to provide a low melting crystalline solid 15 that reacted with 4-chlorotoluene, 4-bromo benzaldehyde and 4-bromoaniline to provide *N*-(4-hydroxyphenyl)-4-methyl benzene sulphonamide 17a, *N*-(4-formylphenyl)-4-methylbenzenesulphonamide 17b and *N*-(4-

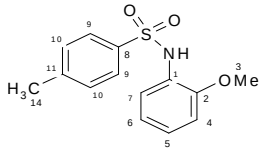
aminophenyl)-4-methylbenzenesulphonamide 17c as oily liquids. Spectral and elemental analytical data are in agreement with the assigned molecular structures. The IR band (cm^{-1}) for -SO_2NH appeared at 1166, 1172 and 1159 for compounds 17a, 17b and 17c , respectively. The nuclear magnetic resonance signals for –CH_3 integrated for three protons as singlets at δ 2.31, 2.32 and 2.33 for 17a, 17b and 17c respectively. Compounds 17a and 17c are oily while 17b is a waxy low melting solid.



	16a	16b	16c
X	Cl	Br	Br
Y	OH	CHO	NH_2

The reaction of compound 15 with 2-chlorotoluene and 1-abromoanisole afforded compounds 4-methyl-*N*-(2-methyl-N-phenyl)benzenesulphonamide 17d and *N*-(2-methoxyphenyl)-4-methylbenzenesulphonamide 17e respectively as waxy low melting and yellow oil. The IR absorption bands for SO_2NH for compounds 17d and 17e were found at 1171 cm^{-1} and 1155 cm^{-1} respectively. The nuclear magnetic resonance chemical shifts for protons in 3–CH_3 and 14-CH_3 in compound 17d were located as singlets at 4.21 ppm and 2.30 ppm. For compound 17e, while the OMe resonate at 4.38 ppm, the -CH_3 proton gave its signal at 2.30 ppm. Other spectral and elemental data are consistent with structural assignments.





Assessment of oral bioavailability property

The physicochemical properties generated by *in-silico* study which were used to assess the possibilities of the synthesized compounds to be bioavailable in the systemic circulation should be formulated and administered orally as a drug. Lipinski "rule of five" (ro5) and total polar surface area (TPSA) were employed to assess the bioavailability of these compounds. Lipinski's ro5 proposed that for a molecule to be drug-like, the molecule should have lipophilicity (log P) ≤ 5, molecular weight (MW) ≤ 500, number of hydrogen bond acceptor (HBA) ≤ 10, and number of hydrogen bond donor (HBD) ≤ 5. The ro5 stipulates that a drug candidate which violates more than one property will have bioavailability problem. According to Table 1, all the synthesized compounds obeyed Lipinski ro5. This, therefore, implies that the compounds have drug-likeness and will be bioavailable should they be formulated as drugs and orally administered. In the same .

Table 1. Physicochemical properties for drug-likeness

Comp	HBA	HBD	NoRB	logP (o/w)	logS	TPSA	MW	LNV
9	4	3	5	1.94	-1.95	83.47	257.31	0
		2						0
10	5		6	1.89	-2.44	91.75	299.35	
11	4	1	6	1.16	-2.72	97.54	298.36	0
13a	5	2	8	2.86	-4.08	103.78	390.46	0
13b	4	2	8	2.49	-4.16	109.57	389.48	0
13c	5	1	9	3.12	-4.49	92.78	404.49	0
13d	5	1	8	2.34	-3.49	96.44	375.45	0
13e	5	1	9	2.27	-4.28	142.26	420.45	0
13f	6	3	8	0.66	-4.01	161.37	406.47	0
17a	3	2	3	2.65	-3.16	66.40	263.32	0
17b	3	1	4	2.88	-3.53	63.24	275.33	0
17c	2	2	3	2.28	-3.24	72.19	262.33	0
17d	2	1	3	3.25	-3.68	46.17	261.35	0
17e	3	1	4	2.91	-3.57	55.40	277.34	0

MW: molecular weight; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; TPSA: total polar surface area; NoRB: number of rotatable bond; LNV: Lipinski's number of violations.

vein, Veber *et al* observed that the number of rotatable bond (NoRB) experimentally influences bioavailability in rats.[27] Therefore, NoRB ≤ 10 is ideal for good oral bioavailability. In this respect, all the compounds obeyed NoRB criteria for drug-likeness. The TPSA is a property used to assess cell permeability of molecules. Generally, TPSA of < 140 Å^2 can easily permeate the cells. Van de *et al* has showed that for a drug molecule to cross the central nervous system (CNS), the TPSA should be ≤ 90 Å^2 [28]. From Table 1, compounds 9, 17a-e have their TPSA ≤ 90 Å^2; and hence, can cross the BBB and can potentially be useful in the treatment of cancerous cells affecting the brain. Table 2 also shows the calculated energies and dipole moments of the synthesized compounds.

Table 2: Calculated energies and dipole moments of compounds

Comp	DM (Debye)	TE (kcal/mol)	EE (kcal/mol)	HOMO (eV)	LUMO (eV)	IP (eV)
9	3.548	-76062.7	-468761	-10.237	-0.747	10.237
10	4.521	-89978.2	-619056	-10.170	-1.007	10.170
11	6.205	-87671.4	-618881	-10.455	-1.212	10.455
13a	3.958	-114026	-914335	-9.180	-0.729	9.180
13b	4.614	-111731	-911755	-8.672	-0.654	8.672
13c	4.730	-117607	-964374	-9.069	-0.716	9.069
13d	3.840	-108129	-859584	-9.429	-0.667	9.429
13e	4.241	-127288	-1001559	-10.101	-1.551	10.101
13f	3.485	-119814	-971421	-9.072	-0.696	9.072
17a	4.838	-73913.2	-452159	-8.954	-0.688	8.954
17b	3.018	-76856.4	-479972	-9.675	-0.922	9.675
17c	7.107	-71615.1	-453037	-8.410	-0.464	8.410
17d	5.403	-70112.7	-454176	-9.494	-0.630	9.494
17f	5.786	-77490.2	-503948	-9.353	-0.569	9.353

DM = Dipole moment; TE = Total energy; EE = Electronic energy (kcal/mol); Homo energy; Lumo energy; IP = Ionization potential

Docking studies

Mutant Human Androgen Receptor (1GS4) derived from an Androgen-Independent Prostate Cancer and Human Mitogen-activated protein kinase 1 (3PP1) are important drug targets for the development of new therapeutic treatments for androgen-independent prostate cancer.[29] These two cancer targets were used in the study to evaluate the binding affinity and chemical interactions of the synthesized compounds with the targets. The result in table 3 reveals that all the synthesized compounds have certain degree of affinity with the targets. There was no significant difference

Table 3: Binding energy (ΔG - kcal/mol) of compounds with different cancer target proteins

Compound	1GS4	3PP1
9	-10.49	-12.00
10	-10.41	-13.21
11	-9.55	-11.28
13a	-12.91	-12.94
13b	-11.29	-11.79
13c	-13.05	-11.55
13d	-11.09	-11.45
13e	-11.08	-10.90
13f	-11.20	-13.34
17a	-11.65	-12.04
17b	-10.23	-10.95
17c	-10.26	-11.27
17d	-9.38	-10.32
17e	-9.80	-10.95
MTX	-12.05	-13.15
Co-CI	-10.92	-11.86

MTX = methothrexate; Co-CI = Co-crystallized inhibitor

between the binding affinity of the standard drug and those of the synthesized compounds, especially 13a-f and 17a-e. This further implies that these compounds can inhibit the replication of cancer cells at different stages. Compound 13c showed highest binding affinity (-13.04 kcal/mol) against 1 GS4 when compared to the standard (-12.05 kcal/mol) and the co-crystallized inhibitor (-10.92 kcal/mol). Similarly, compound 10 and 13f had the highest binding energy (13.21 and -13.34 kcal/mol) against 3PP1 when compared to the standard (-13.15 kcal/mol) and the co-crystallized inhibitor (-

11.86 kcal/mol) (**Table 3**). From the foregoing, it can easily be noted that compounds 13c, 13f and 10 show comparable binding affinity with methothrexate. Therefore, the binding pose of the these compounds and methothrexate in the catalytic sites of the cancer receptors were further studied and the result shown in figures 1-4.

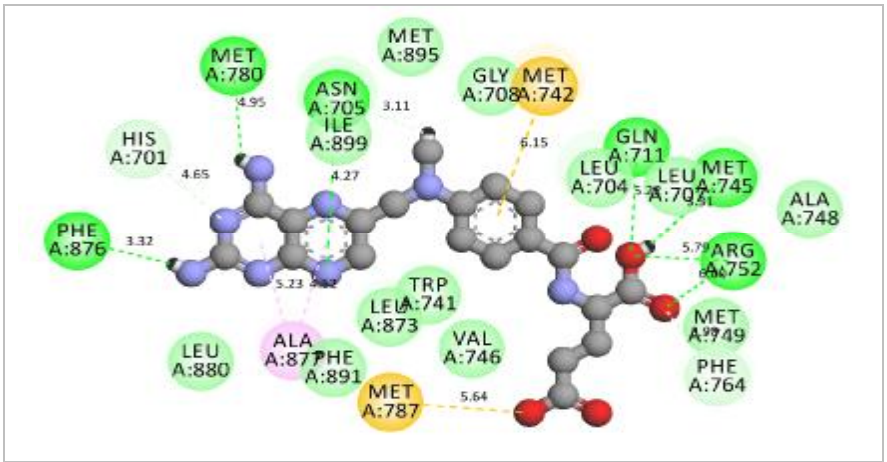


Fig. 1. 3D diagram of 1GS4 interaction with Methotrexate

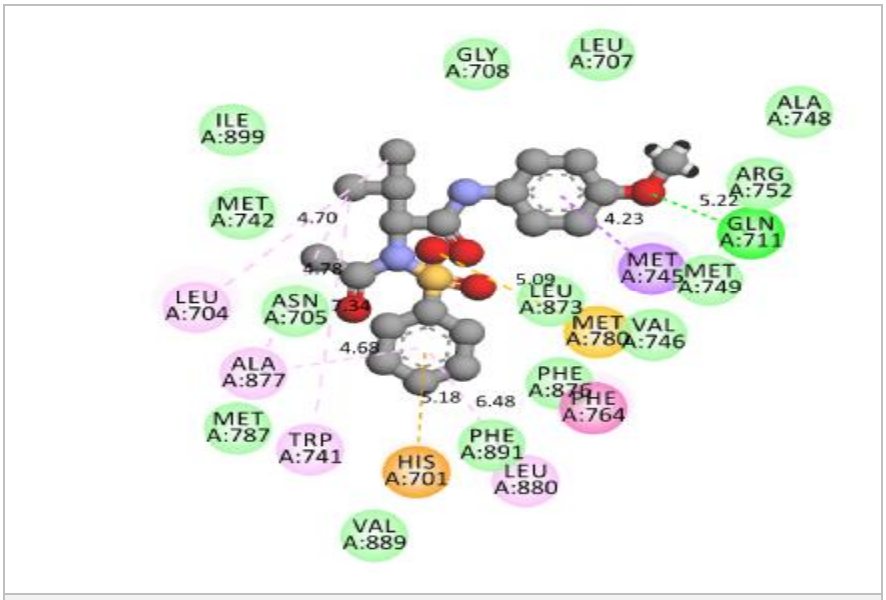


Fig. 2: 3D diagram of 1GS4 interaction with compound 13c

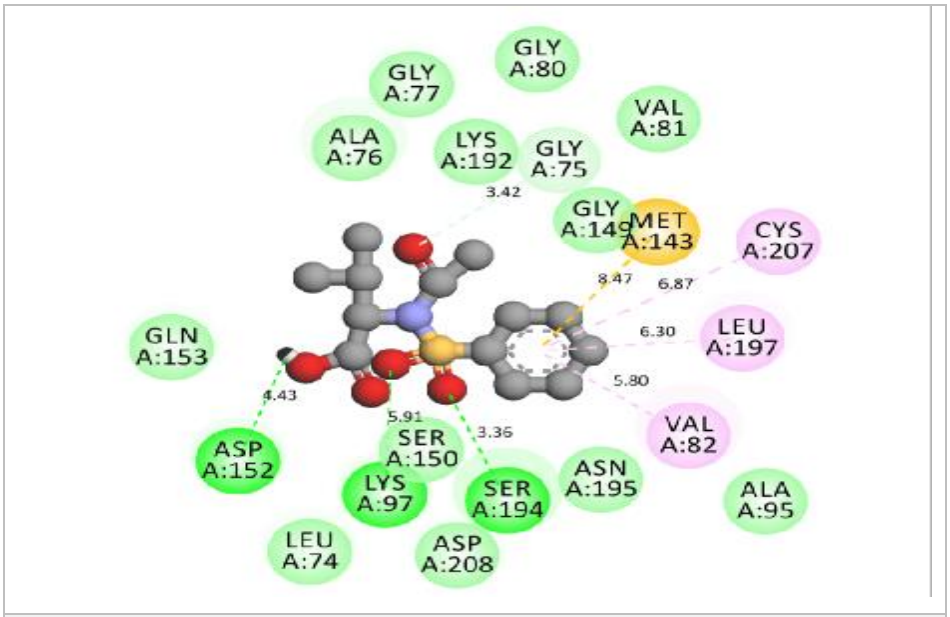


Fig. 3: 3D diagram of 3PP1 interaction with compound 10

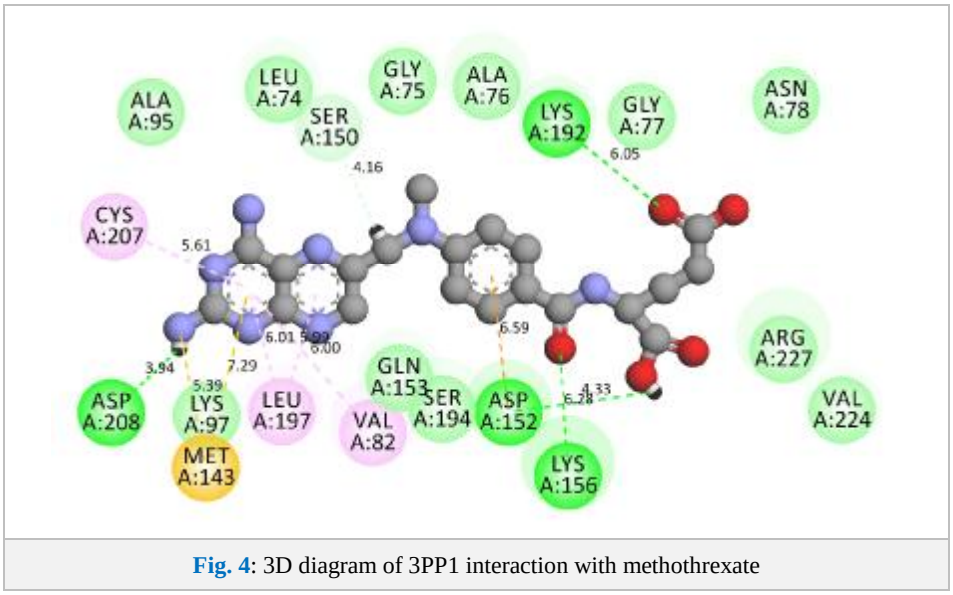


Fig. 4: 3D diagram of 3PP1 interaction with methothrexate

The respective interactions between these compounds and the targets, the ligand atoms and amino acid residues of the receptor cells involved in the interaction and the distance (Å) between the ligand atoms and the residues are shown in figures 1-4 and tables 4a and 4b.

Table 4a: Interactions of methothrexate and compound 13c with 1GS4

1GS4					
Methotrexate			**Comp 13c**		
Active amino acid	Distance of interaction (Å)	Type of interaction	Active amino acid	Distance of interaction (Å)	Type of interaction
MET 780	4.95	H-bonding	MET 780	5.09	Pi-sulphur
PHE 876	3.32	H-bonding	LEU 880	6.48	Pi-alkyl
ALA 877	5.23	Pi-alkyl	ALA 877	4.78	Pi-alkyl
ALA 877	4.52	Pi-alkyl	ALA 877	4.68	Pi-alkyl
ASN 705	4.27	H-bonding	TRP 741	7.34	Pi-alkyl
MET 787	5.64	Pi-sulphur	HIS 701	5.18	Sulphur-X
ARG 752	6.00	H-bonding	LEU 704	5.70	Pi-alkyl
MET 745	3.31	H-bonding	MET 745	4.23	Pi-sigma
GLN 711	5.22	H-bonding	GLN 711	5.22	H-bonding
MET 742	6.15	Pi-sulphur			
ASN 705	3.11	Van der Waals			
ARG 752	5.79	H-bonding			

Table 4b: Interactions of methothrexate and compound 13c with 3PP1

3PP1					
Methotrexate			**Comp 10**		
Active amino acid	Distance of interaction (Å)	Type of interaction	Active amino acid	Distance of interaction (Å)	Type of interaction
CYS 207	5.61	Pi-alkyl	CYS 207	6.87	Pi-alkyl
LEU 197	6.01	Pi-alkyl	LEU 197	5.99	Pi-alkyl
LEU 197	5.99	Pi-alkyl	SER 194	3.36	H-bonding
MET 143	5.39	Pi-sulphur	LYS 97	5.91	H-bonding
MET 143	7.29	Pi-sulphur	MET 143	7.29	Pi-sulphur
VAL 82	6.00	Pi-alkyl	VAL 82	5.80	Pi-alkyl
ASP 152	6.59	Pi-sulphur	ASP 152	4.43	H-bonding
ASP 152	6.28	H-bonding	GLY 75	3.42	Van der Waals
LYS 156	4.33	H-bonding			
LYS 192	6.02	H-bonding			
SER 150	4.16	Van der Waals			
ASP 208	3.94	H-bonding			

Methotrexate is a clinically approved drug for the treatment of various forms of cancers. The binding interactions of methotrexate with the cancer receptors, 1GS4 and 3PP1 have been analyzed and compared to the binding interactions of our synthesized compounds. Though not chemically related, our compounds shared strong and similar binding interactions with methotrexate against the two used receptors. Firstly, with 1GS4 receptor, the common amino acid residues interacted with methothrexate and GLN 711, MET 711, MET 780 and ALA 877. Hydrogen bonding and hydrophobic interactions were involved. The distance of interaction of these amino acids and the atoms of methothexate and 13c were found to be similar. In 3PP1, CYS 207, MET 143, VAL 82, ASP 152 and LEU 197 were the common amino acids involved in the interaction with methothrexate and compound **10.** The details of the amino acid residues interacting with the compounds, their distance of interactions and the type of interactions have been outlined in tables 4a and bb. A study disclosed that MET 143, in addition to other amino acid residues, were responsible for the inhibitory activity of 2-fluoro-4-iodoaniline which was found to bind in the lipophilic pockets of 3PP1.[30]

Conclusion

The synthesis of 2-[acetyl(phenylsulphonyl)amino-3-methylbutanamine 11 and its transformation to various derivatives via Buchwald-Hartwig tandem amidation was

successfully achieved. The synthesized compounds showed strong potential to be possible drug candidates, with compounds 10, 13c and 13f having the highest binding affinity with the cancer receptors.

Experimental

General

All the starting materials and reagents were of technical grade obtained from Sigma-Aldrich and were used without further purification. The melting points were determined with a Fischer John's melting point apparatus and were uncorrected. IR spectra were recorded on a 8400s Fourier Transform Infrared (FTIR) spectrophotometer and were reported in wave number. IR analysis was done at Department of Chemistry, University of Lagos. Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) specrtra were determined using a Jeol 700MH spectrometer at University of Newcastle, United Kingdom. Chemical shifts are reported in (δ) scale. Elemental analysis was carried out with ThermoQuest FLASH series (CHNS) elemental analyzer .

In-silico physicochemical evaluation

The molecular weight (MW), number of rotatable bonds (NoRB), partition coefficient (log P), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD) and TPSA were calculated

using Molinspiration Chemoinformatics software 2016.

Molecular docking studies

Preparation of ligands

ACD/ChemSketch 2015 was used to draw the structures of compounds.[31]

Preparation of protein targets

The 3D crystal structures of two cancer receptor cells namely: Mutant Human Androgen Receptor (pdb code: 1 GS4) and human mutogen-activated kinase 1 (pdb code: 3 PP1) were retrieved from the RCSB Protein Data Bank (PDB) (www.rcsb.org/pdb/home/home.do). All bound ligands, cofactors, and water molecules were removed from the proteins using Discovery Studio Visualizer v16. 1.0. 15350. All file conversions required for the docking study were performed using the open source chemical toolbox Open Babel version 2.3.2 (www.openbabel.org). [32]

Molecular docking experiments

In an effort to identify potential anti-cancer lead (s) among the synthesized compounds, docking calculations using Autodock v4.0.1 into the 3D structure of the catalytic sites of 1gs4 and 3pp1 were carried out.[33] The Gasteiger charge calculation method was used and partial charges were added to the ligand atoms prior to docking.[34] The Lamarckian genetic algorithm (LGA), which is available in Auto Dock was employed.[35] Finally, Auto Dock was used to calculate the binding free energy of a given inhibitor conformation in the macromolecular structure.

Synthesis 2-[Acetyl (phenylsulphonyl)]-3-methylbutanoic acid (10)

To a mixture of acetic anhydride (10 mL) and glacial acetic acid (10 mL) was carefully added to 3-methyl [(phenylsulphonyl) amino] butanoic acid (6 g) and the reaction reflixed at 90 ^{o}C for 45 min. At the end of the reaction, the reaction mixture was cooled to room temperature before being poured directly into 100 mL of cold water and stirred vigorously to obtained shining crystals of the product after filtration. % Yield = 2.52 g (71%), mp 102-104 ^{o}C. IR (KBr) ν_{max}cm^{-1}: 3298(O-H stretch of COOH), 2967,2872 (C-H aliphatic) 1699 (C=O of amide stretch), 1584 (C=C aromatic), 1450,1411 (C-H deformation C $(CH)_2$) 1335 (S=O), 1227 (C-H aromatic) 1166,1141 (C-N) 895,759,728,689 (C-H deformation).^{1}HNMR (d_6-acetone) δ: 7.88-7.87 (m, 5H, ArH), 7.63-7.61 (m, 5H, ArH), 7.58-7.55 (m, 5H, ArH), 6.59 (d, 2H, ArH), 3.787 (s, 3H, CH_3-C=O) 2.15 (m, 1H, CH-$(CH_3)_2$), 0.97 (d, 3H, CH_3-CH), 0.96 (d, 3H, CH_3-CH). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found: C, 52.38; H, 5.18; N, 4.84; S, 10.51.

Synthesis 2-[Acetyl (phenylsulphonyl) amino-3methylbutanamide (11)

A solution of 2-[acetyl (phenylsulphonyl) amino]-3-methybutanoic acid (10 mmol) and *t*-butanol (10 mL) was cooled to 0 ^{o}C. Thionyl chloride (1.10 mL, 1mmol) was added and the entire mixture refluxed for 3 h. The excess thionyl chloride which was evaporated off to obtain a crude acid chloride was dissolved in *t*-butanol (10 mL) and this solution was cooled to 0 ^{o}C. In a separate reaction, *t*-butanol (10 mL) was added to ammonia (0.17 g, 10 mmol) and the mixture was cooled to 0 ^{o}C. The crude acid chloride was then added dropwise to the ammonia solution at such a rate that the temperature was maintained below 5 ^{o}C. Upon completion of the addition of the acid chloride solution, the mixture was shaken intermitently at 0 ^{o}C for 3 h. The reaction mixture was filtered, washed with *t*-butanol and dried to afford the tilled product.Yield = 4.03 g (92%), mp 140-141 ^{o}C. IR(KBr) ν_{max}cm^{-1}: 3262 (NH_2), 1708 (C=O stretch of amide), 1632 (C-N stretch), 2967,2929 (C-H aliphatic), 1585 (C=C of aromatic), 1382 (S=O) 1255,1220,1162,1138 (SO_2 two bonds), 909 (Ar out of plane), 688 (Ar-H). ^{1}HNMR (d_6-acetone) δ: 7.868-7.550 (m, 5H, ArH), 3.595 (s, 2H,NH_2,) 3.083 (s, 3H, CH_3), 1.874-1.353 (d, IH, C-H) , 0.970-0.873 (d, 6H, CH_3). Anal. calcd. for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39; S, 10.75. Found:C, 52.58; H, 6.14; N, 9.84; S, 10.31.

General procedure for the synthesis of the derivatives 13a-f

A mixture of palladium acetate (89 mg, 0.045 mmol), water (5 mmol) and triphenylphosphine (89 mg, 0.045 mmol) was heated for 2 min at 110 ^{o}C in *t*-butanol. Thereafter, potassium phosphate (180 mg, 1 mol), amide (41 mg, 1mol) and aryl halide (250 mg, 1 mol) were added and heating continued under refluxed for 3 h to give the derivatives. These solutions were filtered, the filtrate allowed to evaporate to dryness and

the crude products were re-crystallised from a mixture of *t*-butanol and methanol (1:2) to obtain the pure products. The general procedure was applied in synthesis of compounds 13a-f.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-N-(4-hydroxyphenyl) -3-methylbutanamide (13a)

Compound 2-[Acetyl (phenylsulphonyl) amino-3-methylbutanamide (2) reacted with 4-chlorophenol to provide the titled compound (6) as a yellowish oily compound, yield 86%, bp 121-122 ^{o}C. IR (KBr) cm^{-1} : 3201 (OH aromatic), 3061 (C-H aromatic), 2791 (CH aliphatic), 1492 (C=C aromatic), 1364 (C-H def of C $(CH_3)_2$), 1163 (S=O stretch), 690 (Ar-H).^{1}HNMR (d_6-acetone)δ: 8.211-8.197 (d, 2H, ArH), 7.846-7.712 (m, 5H, ArH), 7.663-7.571 (m, 4H, ArH), 7.363-7.339 (t, 1H, ArH), 7.149-7,082 (m, 5H, ArH), 3.893 (s, 1H, ArH), 3.419-3.318 (m, 1H, C-H), 1.872 (s, 3H, CH_3), 0.961-0.951 (d, 3H, CH_3), 0.860-0.850 (d, 3H, CH_3). ^{13}CNMR (d_6-acetone)δ : 205.615 (C_1), 205.561 (C_6), 157.305 (C_8), 155.987 (C_9), 134.277 (C_{10}), 133.071 (C_{11}), 132.148 (C_{12}), 131.856 (C_{13}), 128.728 (C_{14}), 122.568 (C_{15}), 121.745 (C_{16}), 117.007 (C_{17}), 112.393 (C_{18}), 111.035 (C_{19}), 71.473 (C_2), 63.784 (C_3), 55.564 (C_4), 28.784 (C_5), 28.674 (C_7). Anal. calcd. for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17; S, 8.21. Found:C, 58.38; H, 5.18; N, 8.81; S, 8.51.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-N-(4-aminophenyl)-3-methylbutanamide (13b)

Compound 2-[acetyl (phenylsulphonyl) amino-3-methylbutanamide (2) combined with 4-bromoaniline (41 mg, 250 mg,) to give a titled compound (5) as brownish crystalline solid, yield 72%, mp 115 - 116 ^{o}C. IR (KBr) cm^{-1} : 3332 (N-H stretch of 1^{o} amine), 3056 (C-H aromatic),1620, (C=O stretch of amide), 1591 (N-H bend of 2^{o} amine), 1435 (C-H def asym), 1382 (C=N aromatic), 1282 (C-N stretch of 1^{o} amine), 1162 (S=O stretch). ^{1}HNMR (d_6-acetone)δ: 9.245-9.241 (s, 2H, NH_2), 8.666-8650 (m, 5H, ArH), 7.854-7.706 (m, 4H, ArH), 3.524 (d, 1H, CH), 2.624 (m, 1H, C-H), 1.328(s, 3H,, CH_3), 0.924-0.827 (d, 6H, CH_3).^{13}CNMR (d_6-acetone)δ : 205.425 (C_1), 205.370 (C_5), 156.155 (C_7), 145.353 (C_8), 134.453 (C_9), 131.909 (C_{10}), 131.892 (C_{11}), 131.830 (C_{12}), 131.774 (C_{13}), 128.608 (C_{14}), 128.539 (C_{15}), 127.063 (C_{16}), 125.166 (C_{17}), 62.534 (C_2), 30.426 (C_3), 19.171 (C_4), 18. 184 (C_6). Anal. calcd. for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79; S, 8.23. Found: C, 58.38; H, 5.46; N, 10.88; S, 8.41.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-N-(4-methoxylphenyl)-3-methylbutanamide (13c)

A 2-[acetyl (phenylsulphonyl) amino-3-methylbutanamide (2) reacted with 1-bromo-4-methoxylbenzen to obtained the titled compound (8) as a brownish in colour, yield 85%, mp 191-192 ^{o}C. IR (KBr) cm^{-1}: 2950 (C-H stretch), 2860 (C-H stretch of OCH_3), 1580 (C=C stretch), 1436 (C-H stretch), 1162 (C-N stretch), 704 (Ar-H). ^{1}HNMR (d_6-acetone)δ: 7.825-7.819 (d, 2H, ArH), 7.728-7.700 (m, 5H, ArH), 7.698-7.620 (m, 4H, ArH), 7.582-7.547 (m, 5H, ArH), 3.900 (s, 1H, C-H_3), 3.678-3.142 (d, 1H, C-H), 2.073-2.061 (m, 1H,C-H), 0.9I9-0.909 (d, 3H, CH_3), 0.835-0.825 (d, 6H, CH_3). Anal. calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19; S, 8.54. Found: C, 57.36; H, 5.88; N, 11.37; S, 8.83.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-3-methyl-N- (pyridin-2-yl) butanamide (13d)

A 2-[acetyl (phenylsulphonyl) amino-3-methylbutanamide (2) reacted with 2-chloropyridine to abtained the titled compound **(7).** The compound was yellowish in colour, yield 2.90 g, (91%), 211-212 ^{o}C. IR (KBr) cm^{-1} : 3398 (NH stretch of 1^{o} amine), 3061 (C-H aromatic), 2854 (CH aliphatic), 1481(C=C aromatic), 1389 (S=O stretch), 1321 (C-H def of C $(CH_3)_2$,) 1162 (C-N stretch of 2^{o} amine), 1094, 1049, 996 (C-H of pyridine ring), 691 (Ar-H). ^{1}HNMR (d_6-acetone) δ: 8.783-8.589 (m, 4H, ArH), 7.827-7.644 (m, 5H, ArH), 6.285 (s, 1H, NH), 3.178 (s, 3H, CH3), 2.169-2.159 (d, 1H, C-H), 1.419-1.025 (m, 1H, C-H) 0.990-0.934 (m, 6H, CH_3). Anal. calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19; S, 8.54. Found:C, 57.65; H, 5.53; N, 11.74; S, 8.11.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-3-methyl-N-(6-nitropyridin-2-yl) butanamide (13e)

A 2-[acetyl(phenylsulphonyl)amino-3-methylbutanamide (**2**) reacted with 2-chloro-5-nitropyridine to afford the titled compound (3) as a brick red, yield 81%, mp 127-128 ^{o}C. IR (KBr) cm^{-1} : 3399 (NH), 3055(C-H aromatic), 2922 (CH aliphatic), 1665 (C=O stretch of amide), 1569 (C=N stretch), 1619 (NH bend of NH) 1542 (N=O stretch), 1509 (C=C) 1433 (C-H asym), 1162 (SO_2 two bonds), 1162 (C-N stretch of 2^{o} amine) , 1094, 997 (C-H aromatic) 681 (Ar- H). ^{1}HNMR (d_6-acetone) δ: 7.959-7.810(m, 5H, ArH), 7.794-7.700 (m, 5H, ArH), (7.561- 7.556), 6.641 (s, 1H, ArH), 6.62 (s, 2H, NH_2), 4.849 (s, 1H, NH), 3.900 (s, 1H, CH_3),3.315-3.202 (d, 1H, CH_3-C=O), 2.994-2.061 (m, 1H, CH), 0.941-0.931 (d, 3H, CH_3), 0.852-0.842 (d,3H, CH_3). ^{13}CNMR (d_6-acetone)δ : 205.367 (C_1), 134.488 (C_7), 131,805 (C_8), 131.751 (C_9), 131.493 (C_{10}), 130.273 (C_{11}), 128.623 (C_{12}), 128.585 (C_{13}), 128.518 (C_{14}), 127.095 (C_{15}), 116.045 (C_{16}), 107.210 (C_{17}), 62.969 (C_2), 55.579 (C_3), 31.302 (C_4), 19.185 (C_5), 17.440 (C_6). Anal. calcd. for $C_{19}H_{21}N_3O_6S$: C, 54.41; H, 5.05; N, 10.02; S, 7.64. Found:C, 54.38; H, 5.17; N, 10.64; S, 7.55.

Synthesis of 2-[Acetyl (phenylsulphonyl) amino]-N-(2,6-diaminopyrimidin-4-yl)-3-methyl butanamide (13f).

A 2-[acetyl (phenylsulphonyl) amino-3-methylbutanamide (2) reacted with 6-chloropyrimidine-2,4-diamine to provide the titled compound (4) as a yellowish red, yield 76%, mp 133 - 134 ^{o}C. IR (KBr) cm^{-1} : 3324 (N-H stretch of 1^{o} amine), 1623 (C=O stretch of amide), 1572, (C=N stretch of pyrimidine ring), 1564 (C=C aromatic), 1370 (S=O stretch), 1433 (C-H), 1091,975 (C=H def of pyridine ring), 689 (Ar-H). ^{1}HNMR (d_6-acetone) δ: 7.737-7.704 (m, 5H, ArH), 7.645-7.618 (m, 5H, ArH), 6.75 (s, 1H, ArH), 6.208 (s, 2H, NH_2), 5.921 (d, 1H, C-H), 3.019 (s, 2H, NH_2), 2.103 (m, 1H, CH-$(CH_3)_2$, 1.302 (m, 3H, CH_3-CH), 0.881-0.852 (d, 6H, CH_3-CH). ^{13}C NMR (d_6-acetone)δ : 203.426 (C_1), 165.768 (C_6), 163.528 (C_7), 159.185 (C_8), 131.872 (C_9), 131.858 (C_{10}), 131.823 (C_{11}), 131.768 (C_{12}), 128.601 (C_{13}),

128.533 (C_{14}), 92.718 (C_2), 28.765 (C_3), 28.655 (C_4). Anal. calcd. for $C_{17}H_{22}N_6O_4S$: C, 50.23; H, 5.46; N, 20.68; S, 7.89. Found: C, 50.71; H, 5.10; N, 20.14; S, 8.10.

Synthesis of 4-methylbenzenesulphonamide (15)

A mixture of ammonium hydroxide (1.4 g, 40 mmol) and p-toluenesulphonyl chloride (3.81 g , 20 mmol) was stirred for 5min at room temperature and as the mixture warmed up slightly and thickened to a paste, 20ml of distilled water was added and stirring continued for 3 min. The mixture was further heated on a water bath at temperature of 60 – 70^oC for 2 min and chilled in ice-water. The precipitates formed was collected by filtration, air-dried and recrystalised from aqueous ethanol to give low melting crystalline solid as product, yield = 3.27g (96%), mp 58 – 60 ^oC. IR(KBr) cm^{-1}: 3446, 3337 (N-H stretch for -NH_2), 3072 (C-H of aromatic), 2992, 2942 (C-H of aliphatic), 1585 (C=C), 1373 (S=O), 1172 (SO_2NH), 650 (para substituted benzene). ^1H NMR (DMSO-d_6) δ: 14.51 (s, 2H, -NH_2), 7.51 (d, J=7.86 Hz, 2H, Ar-H), 7.12 (d, J = 7.86 Hz, 2H, Ar-H), 2.24 (s, 3H, CH_3-). ^{13}C NMR (DMSO-d_6) δ: 144(C_1), 139 ($2C_2$), 130 ($2C_3$), 21(C_5). Anal. calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found:C, 49.88; H, 5.17; N, 8.64; S, 18.41.

General Procedure for Synthesis of para-aryl derivatives of 4-methyl benzene sulphonamide (17a-e).

A mixture of bis (triphenylphosphine) nickel (II) chloride (0.3 g,), triphenylphosphine (0.9 g, 3 mmol, t-butanol (4 mL) and water (2 mL) was refluxed under nitrogen atmosphere with stirring for 1h at a temperature of 110 ^oC until the reaction was completed. The entire mixture was then cooled at room temperature, diluted with ethyl acetate, washed with water to afford aryl substituted *p*-toluenesulphonamide in good yields. These products were purified by recrystallisation from aqueous methanol. The general procedure was applied to prepare compounds 17a-17d.

Synthesis of N-(4-Hydroxyphenyl)-4-methylbenzenesulphonamide (17a)

The compound weighed (1.97 g, 74.9%) as a clear oil. IR (KBr) cm^{-1}: 3084 (C-H of aromatic), 2684, 2796 (C-H of aliphatic), 1594, 1467 (C=C), 1249 (S=O), 1166 (SO_2NH), 1009 (C-O), 724 (para substituted benzene). ^1H NMR (DMSO-d_6) δ: 9.75 (s, 1H, N-H), 7.56 (m, 4H, Ar-H), 6.79 (d, J = 8.70 Hz, 2H, Ar-H), 2.31 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 146 (C_1), 144 (C_2), 143 (C_3), 142 (C_4), 140 (C_5), 139 (C_6), 138 (C_7), 136 (C_8), 22 (C_9). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found:C, 52.38; H, 5.19; N, 4.84; S, 10.31.

Synthesis of N-(4-Formylphenyl)-4-methylbenzenesulphonamide (17b)

The compound weighed (1.90 g, 69%) as a waxy low melting solid. IR (KBr) cm^{-1}: 3393 (N-H), 3060 (C-H of aromatic), 2846 (C-H of aliphatic), 1696 (C=O), 1589, 1440 (C=C), 1307 (S=O), 1172 (SO_2NH), 1011 (C-N), 716 (para substituted benzene). ^1H NMR (DMSO-d_6) δ: 10.0 (s, 1H, N-H), 7.92 (dd, J_1 = 1.93 Hz, J_2 = 8.60 Hz, 2H, Ar-H), 7.59 (m, 4H, Ar-H), 3.80 (d, J = 32.14 Hz, IH, CHO), 2.32 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 145 (C_1), 142 (C_2), 140 ($2C_3$), 138($2C_4$), 134 (C_5), 130 ($2C_6$), 129 ($2C_7$), 128 (C_8), 135 (C_9), 20 (C_{10}). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found:C, 52.38; H, 5.18; N, 4.84; S, 10.51.

Synthesis of N-(4-Aminophenyl)-4-methylbenzenesulphonamide (17c)

The compound weighed (2.04 g, 78%) as a thick black oil. IR(KBr) cm^{-1}: 3441 (N-H stretch of NH_2), 3055 (C-H stretch of aromatic), 2910 (C-H stretch of aliphatic), 1613, 1472 (C=C), 1308 (S=O), 1159 (SO_2NH), 1019 (C-N stretch), 710 (para-substituted benzene). ^1H NMR (DMSO-d_6) δ: 7.63(m, 3H, Ar-H), 7.33 (d, J = 8.19 Hz, 2H, Ar-H), 7.12 (m, 4H, Ar-H), 5.27 (s, 1H, NH), 2.33 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) δ: 146 (C_1), 143($2C_2$), 141 ($2C_3$), 139 (C_4), 133(C_5), 129 ($2C_6$), 128 (C_7), 126(C_8), 22(C_9). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found:C, 52.38; H, 5.18; N, 4.84; S, 10.51.

Synthesis of 4-Methyl-N-(2-Methyl-N-phenyl)benzenesulphonamide (17d)

The compound weighed (1.56 g, 59%) as a waxy low melting solid. IR (KBr) cm^{-1}: 3401 (N-H), 3057 (C-H of aromatic), 1668 1452 (C=C), 1319 (S=O), 1171 (SO_2NH), 1016 (C-O), 705 (para substituted benzene). ^1H NMR (DMSO-d_6) δ: 7.57 (m, 4H, Ar-H), 4.21 (s, 3H, CH_3-Ar), 2.30 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 145(C_1), 140 (C_2), 138(C_4), , 136 (C_5), 133 (C_6), 132 (C_7), 130 (C_8), 129 (C_9), 128 (C_{10}), 127 (C_{11}), 126(C_{12}), 22 (C_3), 21 (C_{13}). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found:C, 52.38; H, 5.18; N, 4.84; S, 10.51.

Synthesis of N-(2-Methoxyphenyl)-4-methylbenzenesulphonamide (17e)

The compound weighed (1.99 g, 72%) as yellow oil. IR (KBr) cm^{-1}: 3403 (N-H stretch), 3056 (C-H of aromatic), 2945, 2852 (C-H of aliphatic), 1687, 1588, 1462 (C=C), 1274 (S=O), 1155 (SO_2NH), 1033 (C-O), 726 (para substituted benzene). ^1H NMR (DMSO-d_6) δ: 7.62 (m, 4H, Ar-H), 7.52 (dd, J_1 = 2.38 Hz, J_2 = 7.09 Hz, 4H, Ar-H), 4.38 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3-Ar). ^{13}C NMR (DMSO-d_6) δ: 145 (C_2), 142 (C_1), 140 (C_8), 138 (C_{11}), 136 (C_{10}), 133(C_9), 132 (C_4), 131 (C_5), 130 (C_6), 129 (C_7) , 21 (C_3), 20 (C_{14}). Anal. calcd. for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found:C, 52.38; H, 5.18; N, 4.84; S, 10.51.

References

1. M.J. Yelland, C.J. Nikles, N. McNairn, C.B. Delmar, P.J. Schulter, R.M. Brown, *A series of Rheumatology*, **2004**, 46:135.
2. G. Loncode, N. Pommery, V. Depreux, J. Enzyme, *Inhibitor Med. Chem*., **2003**, 5:18
3. R. Ronn, Y.A. Sabnis, T. Gossas, E. Akerblom, U.H. Danielson, A. Hallberg, A. Johnson, *Bioorg. Med. Chem. Lett*., **2006**, 14:544
4. P. Verhaeghe, N. Azas, M. Gasquent, S. Hutter, C. Ducros, M. Laget, S. Rault, P. Rathelot, P. Vanelle, Bioorg. *Med. Chem. Lett*., **2008**, 18:396.
5. L.L. William, *JAMA*., **2000**, 346:393

6. F.C. Hans, E. Jawetz, *B. G (Ed) Appleton Lange*, **1998**, 4, 761.
7. J. Kumes, J. Bazant, M. Pour, K. Waisser, M. Slosarek, J. Janota, *Farma co*, 55 (**2000**) 725 – 729.
8. D.W. Hopper, M.D. Vera, J. Sabatini, J.S. Xiang, M. Ipeg, *Bioorg. Med. Chem. Lett.*, **2009**, 19:2487.
9. J. De Ruiter, R.F. Borne, C.A. Mayfield, *J. Med. Chem.*, **1989**, 32:145.
10. U.J. Doxepine, *Elsevier*, **2006**, 81-84.
11. K.A. Jones, M. Hatori , L.S. Mure, J.R. Bramley, R. Artymyshyn , S.P. Hong , M. Marzabadi , H. Zhong , J. Sprouse, Q. Zhu, A.T. Hartwick, , P.J. Sollars, G.E. Pickard , S.Panda , *Nat. Chem. Biol.*, **2013**, 9, 630.
12. R.D. Tung, M.A. Murcko, G.R. Bhisetti, Sulphonamides inhibitors of HIV-Asparty Protease (**2007**) EP0659181, US 5585397.
13. O. Skold, Sulphonamide resistance: mechanisms and trends, Drug resistance updates, **2000**, 3, 155.
14. O. Skold, Resistance to trimethoprim and sulphonamides, Veterinary research, **2001**, 32:261.
15. G.A. Khodarahmi, C.S. Chen, G.H. Hakimelahi, C.T. Tseng, *J. W. Chen., J. Iranian Chemistry Society*., **2005**, 2, 124.
16. U.R. Aziz, T. Wajecha, A.A. Muhammed, A. Sumbal, M.K. Khalid, A. Muhammed, A. Hukhar, *Int. J. Chem. Res.*, **2011**, 3, 99.
17. D. Steinhilber, *Curr. Med. Chem*., **1999**, 6, 71.
18. R.S. Vardanyan, V.J. Hruby, *Elsevier*, 2006, 21, 277.
19. L. Beregi, P. Hugon, Sythesis of Essential Drugs, **1971**, 3, 565.
20. S.S. Rindhe, B.K. Karale, R. Gupta, M.A. Rode, *Indian J. Pharm Sci*., 2011, 73, 292.
21. S.M. Sondhi, R. Rani, O.P. Gupta, S.K. Agrawal, A.K. Sexena, *Mol. Divers.*, **2009**, 13, 357.
22. N.A. Nassir, Y.A. Mohammed, A. Zanariah, *Molecules*, **2013**, 18, 11978.
23. B.P. Navin, N.P. Virendra, R.P. Hemant, M.F. Shaikh, J.C. Patel, Acta Pol. Pharm., **2010**, 3, 267.
24. Z. Chen, W. Xu, K. Lu, S. Yang, H. Fan, P. S. Bhadurg, D. Hu, Y. Zhang, *Molecule* **2010**, 15, 9046.
25. D.I. Ugwu, U.C. Okoro, P.O. Ukoha, S. Okafor, A. Ibezim, N.M. Kumar, *Eur. J. Med. Chem.*, **2017**, 135, 349.
26. S. Ali, A.J. Qasir, K.Y. Saor, *Iraqi J. Mark. Rec. Cons. Protection.*, 2009, 1, 1.
26. D.F. Veber, S.R. Johnson, H.Y. Cheng, B.R. Smith, K.W. Ward, K.D. Kopple, *J. Med. Chem*., **2002**, 45, 2615. doi: 10.1021/jm020017n PMID: 12036371
27. W.H. de Van, G. Camenish, G. Folkers, J.R. Chretien, O.A. Raevsky, *J. Drug. Target*., **1998**, 6, 151. doi: 10.3109/10611869808997889 PMID: 9886238
28. Q. Dong, D.R. Dougan, X. Gong, P. Halkowycz, B. Jin, T. Kanouni, S. M. O'Connell, N. Scorah, L. Shi, M.B. Wallace, F. Zhou, *Bioorg. Med. Chem. Lett.*, **2011**, 21, 1315. DOI: 10.1016/j.bmcl.2011.01.071
29. S.D. Barrett, A.J. Bridges, C.M. Flamme, M. Kaufam, A.M. Doherty, R.M. Kennedy, D. Marston, W.A. Howard, Y. Smith, J. S. Warmus, H. Tecle, D.T. Dudley, A.R. Saltiel, J.H. Fergus, A. M. Delaney, S. Lepage, W.R. Leopold, S.A. Przybranowski, J. Sebolt-Leopold, K. Van Becelaere, *Bioorg. Med. Chem. Lett*., **2008**, 18, 6501.
30. ACD/Structure Elucidator, version 15.01, Advanced Chemistry Development, Inc., Toronto, ON, Canada (www.acdlabs.com, 2015.)
31. N. O'Boyle, M. Banck, C.A. James, C. Morley, T. Vandermeersch, G.R. Hutchchison, *J. Chemoinformatics*., **2011**, 3:33. doi: 10.1186/1758-2946-3-33.
32. S.P. Dilber, Z.S. Žižak, T.P. Stojković, Z.D. Juranić, B.J. Drakulić, I.O. Juranić, *Int. J. Mol. Sci*., **2007**, 8:214.
33. J. Gasteiger, M. Marsili, *Tetrahedron*, **1980**, 36:3219
34. G.M. Morris, D.S. Goodsell, R.S. Halliday,R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, *J. Comput Chem*., **1998**, 19, 1639.

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