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FRONTIERS IN CHEMICAL AND LIFE SCIENCES

ISSN: (3065- 4238)

https://multisciajournals.com/journals/index.php/fcls
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Frontiers in Chemical and Life Sciences

Volume 1 Issue 1 2025

The Production of Phenyl Sulphonylamino Alkanamides and N-aryl P-toluene sulphonamides with Potential Medical Use

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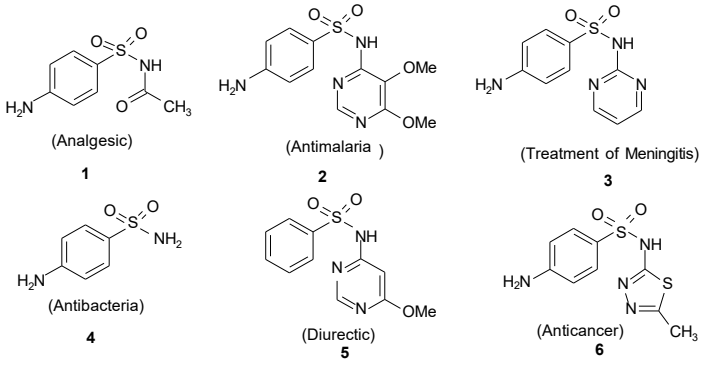
Article Info

Received: 30-01-2025 ***Revised:08-03-2025*** ***Accepted:16-03-2025*** ***Published:27-03-2025***

ABSTRACT

We present the synthesis of N-aryl p-toluene sulphonamides and novel phenylsulphonyl aminoalkanamides, both of which have major medical applications. A product of the reaction between benzenesulphonylchloride 7 and valine was 3-methyl-2-[phenylsulphonyl)amino]butanoic acid 9. This compound was further modified into 2- [acetyl (phenylsulphonyl) amino]-3-methyl butanoic acid 10 by the use of acetic anhydride in acetic acid. The 11th intermediate, 2-[N-acetyl (phenylsulphonyl) amino]-3-methyl butanamide, was produced by reacting the latter with SOCl2 and the former with NH3. Multiple phenyl sulphonylaminoalkanamides 13a–c were produced by reacting the intermediate with commonly accessible aryl chlorides and bromides in a palladium-catalyzed process. 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. Spectroscopic and elemental analytical results validated the structures of the produced substances.

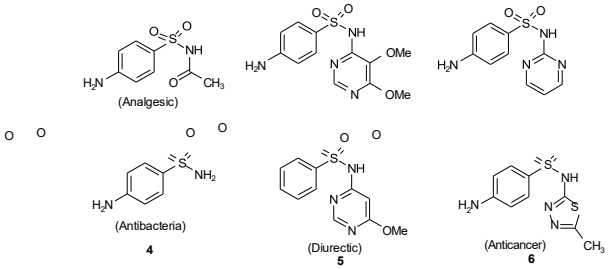
GRAPHICAL ABSTRACT



Keywords: Sulphonamides Organosulfur Anticancer Methotrexate Synthesis

Introduction

Sulphonamides constitute a class of organosulphur compounds and are extensively used as anticancer[1], antitumour[2],antiviral[3],antimalarial[4],antidiabetic[5] antihypertensive , antituberculosis , antiosteoarthiritis , 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.



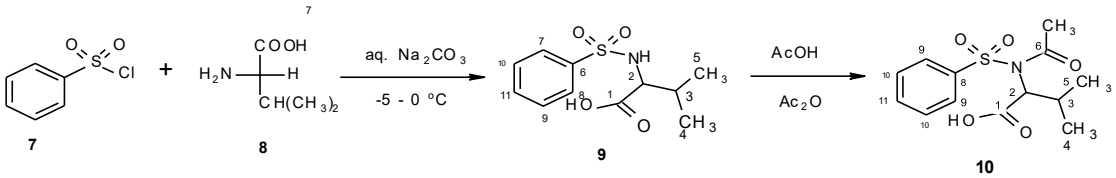
The target of sulphonamide drugs and the basis of their selectivity is the enzyme dihydropteroate synthase (DHPS) in the folic acid pathway.[13] Nowadays, sulphonamides drugs are occasionally used due to horizontal spread of resistance genes, expressing drug-insensitive variants of target enzymes dihydropteroate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

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 synthesisof phenylsulphonylaminoalkanamides and *N*-aryl *p*- toluenesulphonamides as medicinally relevant new sulphonamides.

Results And Discussion

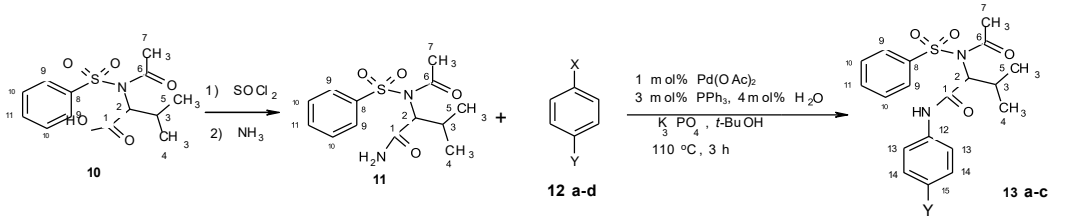
Synthesis

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 ºC, 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 ºC. The spectral and analytical data supported the assigned molecular structure of compound 10.



7 8 9 10

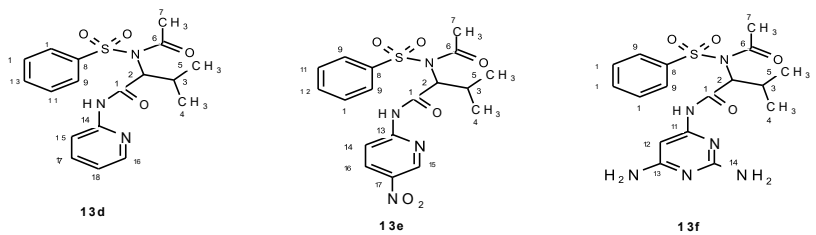
The 2-[acetyl (phenylsulphonyl)]-3-methylbutanoic acid 10 in *t*-butanol was converted into 2-[acetyl (phenylsulphonyl)]-3-methylbutanamide 11 by the reaction with excess thionyl chloride under reflux for 3h affording a black crystalline solid, melting at 140 – 142 ºC. The IR



10 11 12 a-d 13 a-c

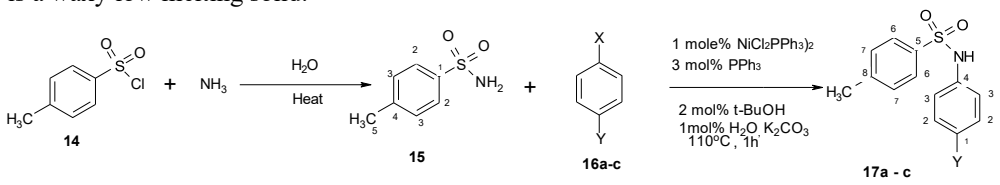
	12a	12b	12c
X	Cl	Br	Br
Y	OH	NH_2	OCH_3

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

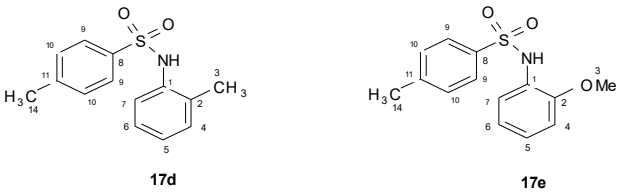
In another development, *p*-toluenesulphonylchloride 14 reacted with ammonium hydroxide in water to provide a low melting crystalline solid 15 that reacted with 4-chlorotoluene,4-bromo benzaldehyde and 4-bromoaniline to provide *N*-(4- hydroxyphenyl)-4-methyl benzene sulphonamide 17a, *N*-(4-formylphenyl)-4-methylbenzenesulphonamide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



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

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

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 adrug 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 orandrogen-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

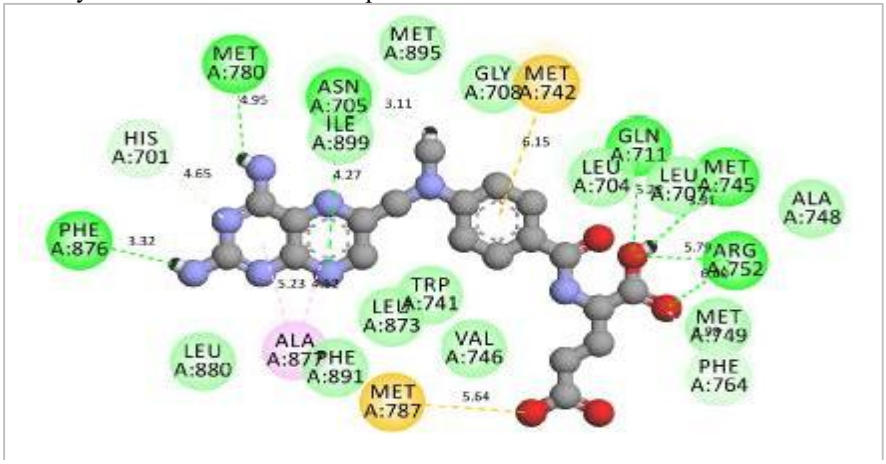
Compound	1GS4	3PP1
9	-10.49	-12.00
13a	-12.91	-12.94
13b	-11.29	-11.79
13c	-13.05	-11.55
13d	-11.09	-11.45
13e	-11.08	-10.90
13f	-11.20	-13.34
17a	-11.65	-12.04
17b	-10.23	-10.95
17c	-10.26	-11.27
17d	-9.38	-10.32
17e	-9.80	-10.95
MTX	-12.05	-13.15
Co-CI	-10.92	-11.86

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

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

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 1GS4 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 thecatalytic sites of the cancer receptors were further studied and the result shown in figures 1-4.



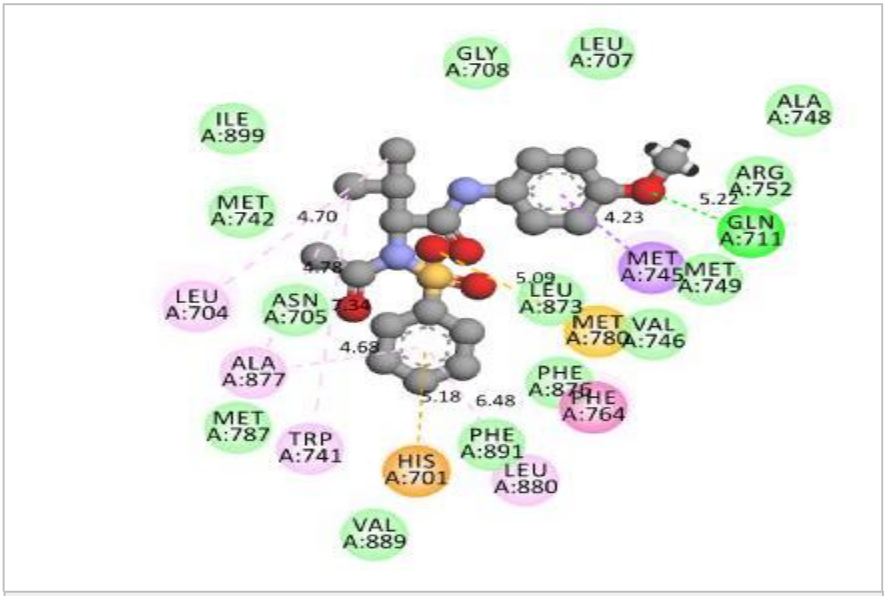


Fig. 2: 3D diagram of 1GS4 interaction with compound 13c

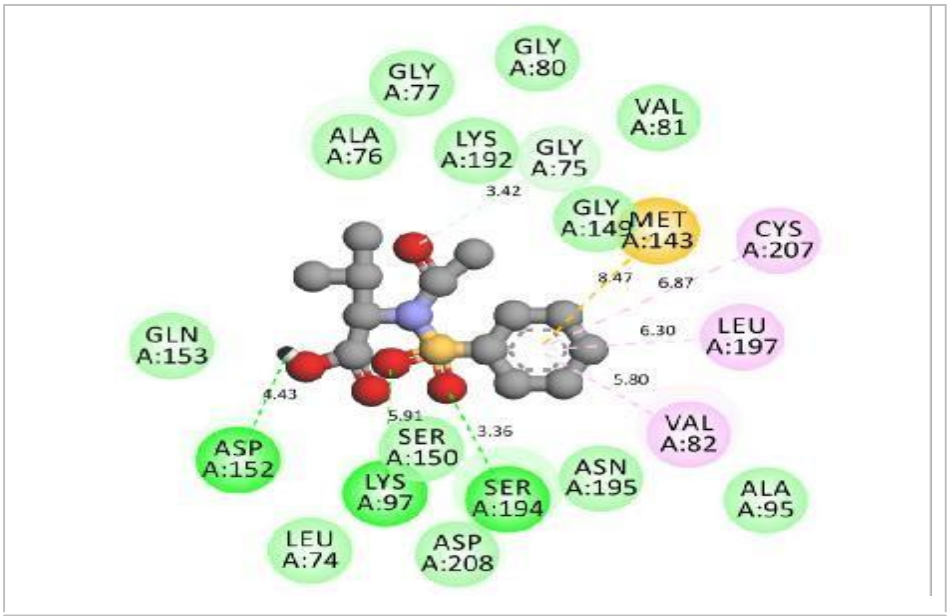


Fig. 3: 3D diagram of 3PP1 interaction with compound 10

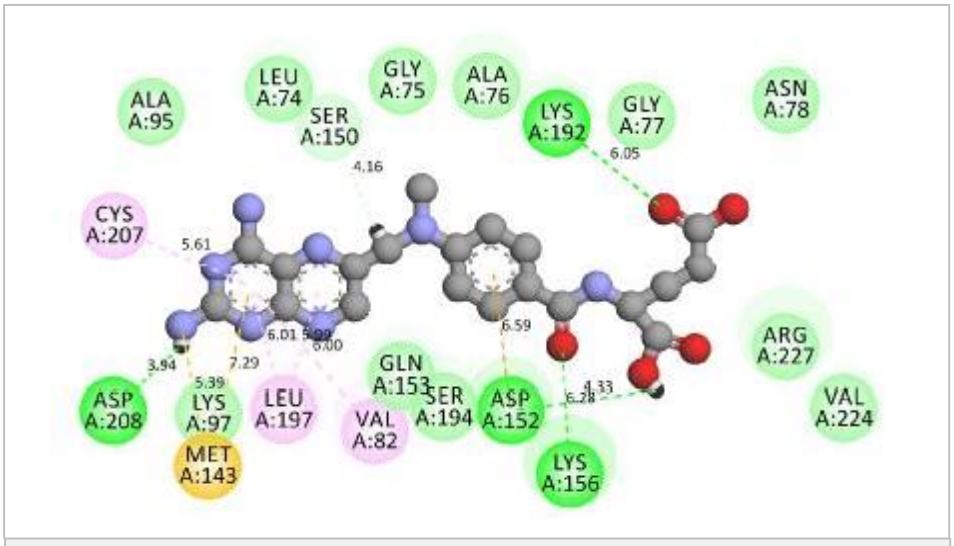


Fig. 4: 3D diagram of 3PP1 interaction with methothrexate

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 infigures 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 theinteraction 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

By using Buchwald-Hartwig tandem amidation, 2-[acetyl(phenylsulphonyl)amino-3- methylbutanamine 11 and its derivatives were synthesized. completed with success. Compounds 10, 13c, and 13f had the greatest binding affinity with the cancer receptors among the produced compounds, suggesting that they may be promising therapeutic candidates.

References

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