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SYNTHESIS, CHARACTERIZATION AND IN VITRO CYTOTOXICITY OF NOVEL ARYLAZO PYRAZOLE DERIVATIVES

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Abstract
A series of novel 3,5-dimethyl arylazo pyrazole derivatives**(3a-h)** were synthesized by the condensation of oxobutyratederivatives **(2a-h)** withp-toluenesulfonyl hydrazide **(1)** in glacial acetic acid medium. Oxobutyrates were prepared from different substituted anilines by diazotization and followed by condensation with acetylacetone in alcoholic medium. All the synthesized compounds were screened for their In-vitro cytotoxicity against MCF-7 and MDA-MB-231 human cell lines and some of the tested compounds **3g, 3h** showed moderatecytotoxicityactivity .All the new compounds were characterized by^{1}H-NMR, IR, Mass spectral data. In order to understand the interactions with active binding site of receptor, Molecular docking studies were also performed

Key words: Pyrazole, oxobutyrates, Cancer, Cytotoxicity, MTT assay

Introduction
Cancer is the name given to a large group of related diseases, which can affect almost any part of the body. It occurs when damaged cells,failed to undergo self-destruction and instead they grow, proliferate and spread abnormally [I]. Disruption of the normal regulation of cell cycle progression and proliferation are the major events leading to cancer. The excess cells so formed may continue to divide indefinitely and form growths called tumour which tend to metastasize in some cases [II]. The tumour micro-environment and the stress signals, such as those caused by damaged DNA, are the regulating factors, that determine whether cancer cells proliferate or die [III].

Heterocyclic chemistry is an ever-evolving field. The quest for new anticancer drugs is underway all over the world and the heterocyclic compounds serve as key structural components for this process [IV].Pyrazole ring has attracted much attention due to its presence in Antipyrine. In recent years, pyrazole systems, have attracted more attention as biomolecules due to their interesting biological activities [IV]. A number of drugs containing pyrazole as main

nucleus available in the market, which possess good pharmacological as well as physiological properties. The presently available pyrazole molecules includesCelecoxib as an anti-inflammatory agent, CDPPB as an antipsychotic agent, Difenamizole as an analgesic agent, Betazole as a H_2receptor agonist, Fezolamine as an antidepressant, Lozanolac as an anti-inflammatory agent, Rimonabant as an antiobesity agent, Mepirizole as an anti-inflammatory agent[V].

The literature of Pyrazoles is enriched with diversified activities. They are reported to possess various biological activities like antibacterial[VI],anti-inflammatory[VII], antioxidant[VIII], anti-tumor[1X], analgesic[X], anti-tubercular[XI], etc., At present Ruxolitinib&Crizotinibare the currently available drugs in the market as antitumor agents containing pyrazole moiety and plays a vital role in influencing the activity [XII]. One of the compound CAN508, is currently emerged as a new anti-proliferative agent with azo and pyrazole group having some sort of selectivity for cancer cells [XII- XIV].

Similarly compounds having hydrazanoor azo groups are able to display a wide range of biological activities. The literature shows the importance of substitution of azo compounds on the various heterocyclic compounds, in increasing the biological potency The incorporation of azo group directly enhances the activity and they are reported with various activities like anti-HIV [XV]and antimicrobial [XVI]properties.

Keeping in view, of the above facts and the biological importance of aryl hydrazono group, and in continuation of work on 3,5-dimetyl arylazo pyrazoles [XVII-X1X], in the present work we report the synthesis and cytotoxicity evaluation of a new series of 3,5-dimetyl arylazo pyrazoles.

EXPERIMENTAL

Melting points were determined using open capillary tube method and are uncorrected. Alpha bruker FT-IR- Spectrometer was used for recording IR spectra (cm^{-1}). Bruker Avance-II NMR spectrometer (USA) was employed to record ^{1}H-NMR spectra operating at 400 MHz with DMSO/$CDCl_3$ as a solvent. TMSwas served as an internal standard. The recording of the mass spectra was carried out by Perkin -Elmer GC-MS**.**TLC plates were used to monitor the progress of the chemical reaction.

General procedure for Synthesis of 3-5-dimetyl arylazo pyrazole derivatives (3a-h)

A mixture of oxobutyrates**(2a-h)** and p-toluenesulfonyl hydrazide **(1)** were dissolved in 30 ml of glacial acetic acid. The reaction contents were refluxed for about 16-22 hrs and poured into the crushed icewith vigorous stirring.. The resulted precipitated compound is filtered and recrystallized from suitable solvents [XVII]. The physical data of the compounds is given in table-1.

4-((4-chlorophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole (3a): IR(KBr,cm^{-1}): 1357(SO_2), 1422(N=N),1514(C=C), 1623 (C=N), 3101 (C-H). **^{1}H-NMR($CDCl_3$):** 2.30 (s, CH_3,3H), 2.37 (s, CH_3,3H), 2.47 (s, CH_3, 3H), 7.43-7.59(m, Ar-H, 8H). **MS (m/z):**388.87 (M+).

4-((4-bromophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole (3b): IR(KBr,cm^{-1}): 1359,(SO_2), 1424(N=N),1505(C=C), 1623 (C=N), 3066 (C-H). **^{1}H-NMR($CDCl_3$):** 2.34 (s, CH_3,3H), 2.37 (s, CH_3,3H), 2.47(s, CH_3, 3H), 6.99-7.61(m, Ar-H, 8H). **MS (m/z):**433.42(M+).

4-((4-fluorophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole (3c): IR(KBr,cm^1) : 1388(SO_2), 1468(N=N), 1583(C=C), 1627 (C=N), 3089 (C-H). **^{1}H-NMR($CDCl_3$):** 2.37 (s, CH_3,3H), 2.41 (s, CH_3,3H), 2.47(s, CH_3, 3H), 7.03-7.62(m, Ar-H, 8H). **MS (m/z):**372.32(M+).

3,5-dimethyl-4-((4-nitrophenyl)diazenyl)-1-tosyl-1H-pyrazole :(3d): IR(KBr,cm^{-1}): 1320(SO_2), 1487(N=N),1548(C=C), 1586 (C=N), 3002 (C-H). **^{1}H-NMR($CDCl_3$):** 2.31 (s,

CH_3,3H), 2.36(s, CH_3,3H), 2.44(s, CH_3, 3H), 7.16-8.34(m, Ar-H, 8H). **MS (m/z):**399.42 (M+).

4-((2,4-dinitrophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole:(3e): IR(KBr,cm^{-1}): 1360(SO_2), 1474(N=N), 1510(C=C), 1590 (C=N), 2924 (C-H). **^{1}H-NMR($CDCl_3$):** 2.30 (s, CH_3,3H), 2.36 (s, CH_3,3H), 2.47(s, CH_3, 3H), 7.07-8.35(m, Ar-H, 7H). **MS (m/z):**444.42(M+).

3,5-dimethyl-4-((4-methyl-2-nitrophenyl)diazenyl)-1-tosyl-1H-pyrazole:(3f): IR (KBr,cm^1): 1391(SO_2), 1475(N=N), 1510(C=C), 1597 (C=N), 2987 (C-H). **^{1}H-NMR($CDCl_3$):** 2.31 (s, 2xCH_3,6H), 2.47(s, 2xCH_3,6H), 7.17-7.43(m, Ar-H, 7H). **MS (m/z):**413.45 (M+).

4-((3,4-dichlorophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole:(3g): IR(KBr,cm^{-1}): 1402(SO_2), 1496(N=N),1553(C=C), 1591(C=N), 3065(C-H). **^{1}H-NMR($CDCl_3$):** 2.31 (s, CH_3,3H), 2.36 (s, CH_3,3H), 2.47(s, CH_3, 3H), 7.16-7.42(m, Ar-H, 7H). **MS (m/z):**423.32 (M+).

4-((2-chloro-4-fluorophenyl)diazenyl)-3,5-dimethyl-1-tosyl-1H-pyrazole:(3h):IR(KBr,cm^{-1}): 1395(SO_2), 1458(N=N), 1550(C=C), 1595 (C=N), 3066 (C-H). **^{1}H-NMR($CDCl_3$):** 2.38 (s, CH_3,3H), 2.44 (s, CH_3,3H), 2.47(s, CH_3, 3H), 7.01-7.88(m, Ar-H, 7H). **MS (m/z):**406.86(M+).

In silico analysis

Schrodinger 2018-3 suite device Maestro 11.7.012, (Ligprep, Glide XP docking, QikProp) was used for In-silico analysis (Lipinski's RO5, molecular docking, ADMET properties [XX]. Docking of the synthesized compounds was carried out in the groove of binding site of 2QP6, which is the crystal structure of bioreductive antitumor derivative.

MTT ASSAY

Cell lines and culture condition

The cytotoxicity of the synthesized pyrazole derivatives**(3a-h)** were determined by the MTT assay. The required cell lines were purchased from National Chemical Laboratory, Pune, India. Both the cell lines were maintained with very small amounts of DMEM supplemented with 5% of FBS and 1% antimycotic- antibiotic- solution. The cells were maintained at 37 °C in a humid atmosphere containing 5% CO_2.

Procedure

The MTT assay was carried on a 96 well flat bottom micro titer plates. The cells (MDA-MB231 and MCF-7) were seeded onto the plates with a density of 5,000 cells/well, permitted to adhere and further incubated overnight in the humid atmospheric conditions. All the new compounds were tested at a concentration of 6.25, 12.5, 25, 50 and 100 µM. The cell reaches the confluence, after 48hours incubation. 100 mL of MTT solution (1 mg/mL) was added to the wells, after the incubation [XX1]. The absorbance was recorded at 570nm with a with ELISA reader and percentage cytotoxicity was calculated in comparison with control. The cytotoxicity IC_{50} (µM) of the compounds **(3a-h)** is given in Table-2.

Results and Discussion

Chemistry

The reaction sequence is depicted in **Scheme-01.**The key intermediateoxobutyrates**(2a-h)** were prepared as per the reported procedure[XVIII] by diazotization of substituted aromatic anilines followed by condensation with acetyl acetone in the alcohol medium. The title compounds**(3a-h)** were synthesized by reacting oxobutyrates**(2a-h)**and p-toluene sulfonyl hydrazide**(1)**in glacial acetic acid medium. The physical data of the compounds is showed in table-1. The progress of the reaction is monitored by TLC (ethyl acetate: methanol9.5:0.5) and all the compounds were recrystallized by using alcohol.

The structures of the new compounds were established on the basis of ^{1}H-NMR, Mass and IR spectral data. The IR spectrum of compound **3a**exhibited characteristic absorption bands at 3101 cm^{-1}due to the C-H functional group.The other important groups were observed at 1623 cm^{-1} (C=N), 1422 cm^{-1}(N=N), 1357 cm^{-1}(SO_2) respectively. In the ^{1}H-NMR spectra of the compound, **3a**revealed the singlet signals for methyl protons at δ 2.30, 2.37, 2.47 region respectively. The aromatic protons were observed as multiplets in the region δ 7.45-7.59. The mass spectrum of compound**3a**, showed the appearance of molecular ion peak at 404.87 which is consistent with the assigned molecular formula.

In-vitro cytotoxicity study

The MTT assay was carried out in order to determine the cytotoxic effect of the newly synthesized compounds on cancerous cell lines. The cytotoxicity of all the synthesized compounds were performed against MCF-7 and MDA-MB-231 cell lines using MTT colorimetric assay.The results of the MTT assay is showed in Table-2. Some of the tested compounds displayed weak to moderate cytotoxicactivity against both the cell lines. The percentage inhibition in cell proliferation at an IC_{50} value varied from 24.16 to 45.11 µM.

The anticancer results revealed that, some of the tested compounds (3a, 3b 3h)displayed moderate activity against MDA-MB cell lines. Most of the tested compounds showed moderate activity. The activity may be due to the presence of electron withdrawing groups (chloro, bromo) present at the position -2.

When the compounds were tested against MCF-7 cell lines, some of tested compounds (3f, 3g, 3h) showed moderate activity.The compounds due to the presence of electron withdrawing groups, are responsible for the activity.

In-silico analysis

In accordance to the Lipinski's RO5, partition coefficient ≤5, the molecular weight of the molecule should be ≤500, the number of hydrogen bond donors and acceptors should be ≤5 and ≤10, respectively. The rule also states that the polar surface area (PSA) ≤140 Å. Along withthe molecular flexibility and the above parameters are found to be essential for the oral bioavailability of the compounds. Hence, the evaluation of the compounds ability to obey this rule was evaluated. Moreover, other physiological parameters such as % human oral absorption, QPPlog BBB, QPlogKhsa, QlogKp, and QPPCaCO-2were predicted, studied and reported in Table-5.

The compounds had the desired physicochemical characteristics (Table-3), having no deviations from the standard ranges. The number of rotatable bonds (Nrobs) measuring the molecule's flexibility and a good indicator of drug absorption and bioavailability were within the acceptable limit of 10 for all the compounds. tPSA is regarded as the capability of a molecule to undergo hydrogen bond formation. The tPSA values of all the compounds were within the limit of 140 Å indicating good cell permeability and gives an insight into the hydrogen bonding potential of the compounds. In case the tPSA values were>140 Å , it would indicate that the drugs have poor absorption. The synthesized compounds obeyed Lipinski's rule of five , since all the values were observed within the acceptable limits. (Table-3).

Compounds (3a-h) possessed hydrogen bond donors and hydrogen bond acceptors in the range of 0-9.5. The affinity of the compoundswith the receptor2QP6 is given in Table-4 in terms of dock score. The binding free energy of the compounds ranges from -2.75-4.43 kcal/mol on docking with 2QP6.

Upon docking, with 2QP6, the active residues were found to be PHE 348, GLY 351, ASN 352, ASP 353, VAL 354, ASP 356, TRP 357, ARG 303, GLY 304, HIE 305, and GLY 306.T LEU 57, ARG 58, ASN 67,GLU 69,PHE 70, ASP 71, ASP 72, ILE 91, GLN 92, ASP 130, PHE 131 and GLY 132. The highest affinity is observed in compound3c, which is having a binding

energy of -4.43 kcal/mol, and compound 3e, showed the binding energy of -3.60 kcal/mol. The docking conformations of compound 3c with 6QP6 are depicted in Fig-1,2.

The ADME studies are reported in Table-5. The predicted Blood Barrier Barrier partition coefficient (Qlog BBB) gives an idea about the penetration of the drug into the CNS. Drugs with very high polarity cannot cross the BBB. The values for all the synthesized compounds fall within the recommended range of -3 to 1.2. QPlogKp score is an indication of skin permeability. All the compounds have good skin permeability as the value of QPlogKp is within the recommended range of -8 to -10. Caco-2 cells are a great model to depict gut-blood barrier and non-active transport. QPPCaco predicts the apparent Caco-2 cell permeability in nm/sec. A value above 500 indicates great intestinal permeability whereas a value below 25 indicates very poor permeability. The predicted values of QPPCaco indicated that the synthesized compounds have good intestinal permeability (except compound 3e) QPlogKhsa score is used to predict the binding of the compounds to the human serum albumin. A higher value indicates that the compound is strongly bound to albumin and hence is not available for activity. All the compounds fall within the recommended range indicating that the binding to the human serum albumin is not strong and hence the compounds are free for activity.

CONCLUSION

In conclusion, the main aim of this present work is to synthesize a new series of 3,5-dimetyl arylazo pyrazole derivatives and screening for their cytotoxicity against various cell lines by In-vitro methods. The structures of all the new compounds were established by spectral data. The cytotoxicity data of the tested compound indicates the presences of electron donating groups are responsible for the cytotoxicity activity.

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Table-1:Physical data of substituted arylazo pyrazoles (3a-h)

Comp	R-NH_2	Molecular Formula	Molecular weight	MP (°C)	Yield (%)
3a	4-Cl	$C_{18}H_{17}ClN_4O_2S$	388.87	99-100	68
3b	4-Br	$C_{18}H_{17}Br\ N_4O_2S$	433.32	125-27	65
3c	4-F	$C_{18}H_{17}FN_4O_2S$	372.42	114-16	66
3d	4-NO_2	$C_{18}H_{17}N_6O_4S$	399.42	145-47	64
3e	2,4-$(NO_2)_2$	$C_{18}H_{16}N_6O_6S$	444.42	131-33	65
3f	2-NO_2-4-CH_3	$C_{19}H_{19}N_5O_4S$	413.45	178-80	63
3g	3,4-$(Cl)_2$	$C_{18}H_{16}N_4O_2SCl_2$	423.32	159-61	62
3h	2-Cl-4-F	$C_{18}H_{16}N_4O_3ClFS$	406.86	140-42	61

Table-2:Cytotoxicity IC_{50} (µM) of compounds (3a-h)

Comp	MDA-MB-231	MCF-7
3a	28.14 ± 0.34	32.12± 0.94
3b	26.11 ± 0.21	28.41± 0.58
3c	32.11 ± 0.16	31.05± 0.14
3d	29.64± 0.19	31.16± 0.67
3e	45.11± 0.54	29.41± 0.27
3f	28.11± 0.28	26.34± 0.75
3g	29.54± 0.49	24.16± 0.42
3h	27.54± 0.37	25.19± 0.31

Table -3: Lipinski's RO5 for compounds(3a-h)

Comp	Molecular weight	Log P(o/w)[a]	Donor HB [b]	Nrobs [c]	Acceptor HB [d]	Rule of 5 (No of violations)
Acceptable range	**≤500**	**≤5**	**≤10**	**(-2.0 to 6.5)**	**≤10**	**≤5**
3a	388.871	2.161	0	4	7.5	0
3b	433.322	2.226	0	4	7.5	0
3c	372.416	3.22	0	4	7.5	0
3d	399.423	2.228	0	5	8.5	0
3e	444.421	1.557	0	6	9.5	0
3f	413.45	2.635	0	5	8.5	0
3g	423.316	3.924	0	4	7.5	0
3h	406.861	3.604	0	4	7.5	0

[a]Log P(o/w)-Predicted octanol/water partition coefficient log P.
[b]Donor HB-The number of hydrogen bonds that would be donated by the compound
[c]Nrobs - Predicted rotatable bonds
[d]Acceptor HB- The number of hydrogen bonds that would be accepted by the compound

Table-4: Dock scores of compounds (3a-h)

Comp	**Dock score**
3a	-2.951
3b	-2.754
3c	**-4.435**
3d	-3.299
3e	**-3.606**
3f	-2.855
3g	-2.923
3h	**-3.467**

Table-5: ADME properties of compounds(3a-h)

Comp	**QlogBBB[a]**	**QlogKp[b]**	**QPPCaco-2[c]**	**QPlogKhsa[d]**	**Percent human oral absorption[e]**
Acceptable range	**(−3 to 1.2)**	**(−8.0 to −10.0)**	**<25 Poor, >500 great**	**(−1.5 to 1.5)**	**>80% High, <25% low**
3a	-0.321	-1.527	1783.54	-0.107	100
3b	-0.311	-1.529	1783.583	-0.081	100
3c	-0.53	-2.1	1064.944	-0.289	100
3d	-0.573	-2.7	664.447	-0.454	90.117
3e	-2.457	-4.678	41.795	-0.474	52.12
3f	-1.361	-2.979	346.829	-0.201	87.835
3g	-0.192	-1.659	1781.318	0.011	100
3h	-0.241	-1.571	1827.962	-0.093	100

[a]Predicted brain/blood partition coefficient.
[b]Predictedskin permeability
[c]Predicted apparent Caco-2 cell permeability in nm/s.
[d]Prediction of binding to human serum albumin.
[e]Predicted percentage human absorption

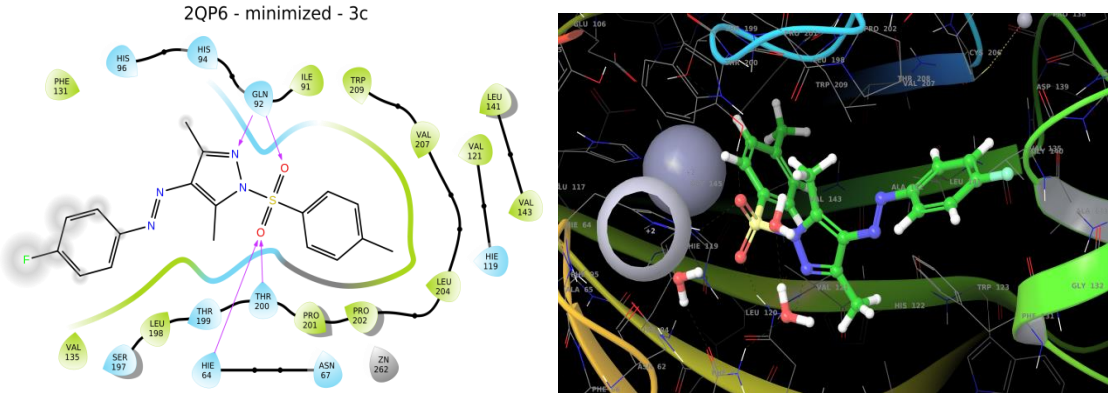

Fig 1: - 2D and 3D interaction of compound **3c** with**2QP6**

Scheme-01