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Preface

We would like to present, with great pleasure, the inaugural volume-6, Issue-7, July 2020, of a scholarly journal, *International Journal of Engineering Research & Science*. This journal is part of the AD Publications series *in the field of Engineering, Mathematics, Physics, Chemistry and science Research Development*, and is devoted to the gamut of Engineering and Science issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Engineering and Science as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical investigations. Its mission is to become a voice of the Engineering and Science community, addressing researchers and practitioners in below areas

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Algorithm and Computational Complexity	Artificial Intelligence
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Information Retrieval	Low Power VLSI Design
Neural Networks	Plastic Engineering

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within that community who supported the idea of creating a new Research with IJOER. We are certain that this issue will be followed by many others, reporting new developments in the Engineering and Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IJOER* readers and will stimulate further research into the vibrant area of Engineering and Science Research.

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Retrofitting of Soft Storey Building by using Different Bracing System due to Seismic Load

Vijay Shankar Sahu[1], Himanshu Shrivastava[2]

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Abstract— *In the present study an attempt has been made to evaluate an existing building located in seismic zone V using equivalent static analysis. Indian Standard IS-1893:2002 (Part-1) is followed for the equivalent static analysis procedure. Building is modeled in commercial software STAAD Pro. Seismic force demand for each individual member is calculated for the design base shear as required by IS-1893:2002. Corresponding member capacity is calculated as per Indian Standard IS456:2000. Deficient members are identified through demand-to-capacity ratio. A number of beams and column elements in the first floor of the present building are found to be deficient that needs retrofitting. A local retrofitting strategy is adopted to upgrade the capacity of the deficient members. This study shows that steel jacketing is an efficient way to retrofit RC members to improve flexure as well as shear capacity.*

***Keywords*— RETROFITT, Earthquake, Composite, Conventional, Frame, Steel, Reinforced Concrete, Structure, Multi-storey, SMRF, Framed structures, Maximum Axial Force, STAAD PRO.(V8i) series 4.**

I. INTRODUCTION

The increase in urbanization for the past few years has made the vehicle parking a major concern. In order to overcome this usually we provide the first storey of the building for parking. The open ground storied structure is a structure in which the infill wall is absent at the ground storey for the purpose of parking or social gathering. According to earthquake reports the structure having open ground storey leads to complete collapse due to absence of infill wall. Distribution of strength, mass, stiffness should be consistent throughout the building both vertically and horizontally as per design philosophy of structures. Improper orientation of walls results in soft storey, weak storey and torsion effect. The severe damage can be seen on the structure due to irregularity of structures. Due to modern era of construction the buildings without open ground storey is unavoidable because there is shortage of area for parking so we have to provide some special measures on the structure to mitigate the effect of soft storey on the structure . It is very necessary to conduct an in-depth study on the nonlinear behavior of the structure so that it gives the proper response of the structure during earthquakes.

II. LITERATURE REVIEW

1. N.A. Ghate and S.P. Siddh (2018) studied various building models such as soft storey structure with shear wall, and soft storey with steel bracings at the first storey. The study includes the analysis of soft storey building with ETABS software by pushover analysis method and the results and conclusion of the analysis is to be included. There are three models- first is Infill frame with soft storey (IFSS), second one is Infill frame with .shear wall in soft storey (IFSW) and third one is Infill frame with cross bracing (IFCB). From the pushover analysis of the structural models the results for maximum base shear, maximum displacement, maximum inter-storey drift, maximum storey force, etc are analyzed. When considered base shear capacity IFSW exhibit higher base shear than other systems irrespective of number of stories. Base shear of G+9 IFSW is higher than the base shear of IFSS, IFCB. Building with shear wall at the bottom storey had higher moment when compared to other systems irrespective of the number of stories. Response reduction factor of these frames is higher than the IS code recommendations. Time period of these systems is more when comparing to IS code time period from IS 1893.

2. R. Ismail, et.al (2018) analyzed 4 models with various bracings system like V bracing, X bracing, eccentric bracing and without bracing. An investigation had been conducted to determine the lateral displacement by using SAP2000. The objectives of this paper are to determine the maximum displacement and base shear on each sort of bracing system. The outcomes were analyzed from time history analysis by various type of bracing system. The result for both maximum displacement and base shear is based on 0.05 second of peak ground acceleration. It can conclude that

model which has V bracing type is the best and effective method of bracing system for soft storey building. From the outcome acquired, it demonstrated that V bracing had the lowest value for maximum displacement compared with other models. In addition, V bracing type also showed the lowest value of base shear. Thus, it proved that V bracing type reduces the maximum displacement and base shear of the soft storey building. X-bracing can reduce lateral storey displacement, storey drift as well as axial force and bending moment in columns effectually.

3. B. Patel, et.al (2017) observed different braced buildings were studied and the seismic parameters in terms of base shear and storey displacement are compared. Also these parameters were analyzed using different types of bracing and to choose appropriate bracing configuration to resist seismic load efficiently. The STADD Pro and ETABs software's were used for modeling and to carry out the analysis. The lateral loads subjected to the buildings were considered as per Indian standard codes. Three models were prepared in which first is Moment Resisting Frame (MRF) second is RCC building with V-bracing system and third is RCC building with X- bracing system. The equivalent static load analysis was carried out using STADD ProV8i and the response spectrum analysis was carried out using ETABS. Finally the conclusions are drawn as the base shear of braced buildings increased as compared to building without bracing which indicates that the stiffness of building increases. The performance of X- bracing system has more margin of safety when compared to V-bracing system.

4. A Dharanya, et.al (2017) analyzed a G+4storey residential RC building with soft storey retrofitted with cross bracings and shear wall. This analysis was made as per IS 1893:2002 codal provision by using ETABS software. The cross bracings such as X bracing were to be provided at the outer periphery of the column and the shear walls were provided at the corners of the buildings. The building models were analyzed by equivalent stiffness method using ETABS software. That building was considered to be located at Bhuj, which is one of the high seismic area (Zone V) located in India. To improve the building's stability against lateral loading an additional structural member such as shear wall and bracings were placed in the structure and analyzed. Finally the conclusions was drawn that the natural time period of the structure has highly reduced after placing shear wall than the bracings, which will improve the stability against earthquake and make the structure more stable. The structure has a minimum lateral displacement with shear wall and bracings compared with bare frame. Structure with shear wall system has a least lateral displacement.

5. S. Kiran, et.al (2017) studied the effects of soft storey in the buildings and remedying it by using different structural arrangements, like shear walls, diagonal steel bracing and cross steel bracings. The linear dynamic analysis (response spectrum analysis) had been adopted for various symmetrical buildings such as low rise (G+6), medium rise (G+14) and high rise (G+24). The response of the models, in terms of storey drift, lateral displacement, storey shear and storey stiffness was compared for different configurations resulting that 95% decrease in term of lateral displacement for low rise 95% for medium rise and 95% for medium rise building. It was concluded that the provision of shear walls can reduce the effects of soft storey to a much greater extend. Cross steel bracings can also play an inevitable role in reducing the soft storey effect in the buildings.

III. RESULTS AND DISCUSSIONS

From above literature review it is summarized that the structure with soft storey losses greater initial stiffness and maximum strength when compared to the structure without soft storey. It was also observed that the load path from the point of application of load was not distributed properly in the structure with soft storey. The placement of shear walls can be modified to enhance the performance of building in seismic prone areas. The analysis was done for Zone III and IV, to analyze in higher seismic prone areas it can be done for Zone V.

Also it can be seen that in that shear wall could improve the lateral stability of the structure more than the bracings in a simple framed structures. The different kind of bracings are used in a model and analyzed to determine the best type of bracings which can be effectively used in structure to reduce storey drift, storey displacement etc. From above review X bracings are more effective for minimum storey displacement and also give more margin safety. As the height of the building increases, stability of the building becomes a major factor that can be achieved by using structural configurations. Also we get that the displacement reduces when the soft storey is provided in higher levels.

TABLE 1
SPECIFICATIONS OF BUILDING

S.No.	Description	Specifications
1.	Building Frame System	OMRF
2.	Ground Storey height	3.5m
3.	Typical Storey height	3.0m
4.	Type of soil	Medium (II)
5.	Support Condition	Fixed
6.	Grade of concrete	M30
7.	Grade of steel	Fe 415
8.	Live Load	3.5 kN/m2
9.	Floor Finish	1 kN/m2
10.	Infill Panel	Brick Masonry
11.	Importance factor	1
12.	Response Reduction Factor	3
13.	Column Size	600mm x 300mm
14.	Beam size	500mm x 350mm
15.	Slab Thickness	120mm
16.	Stair Slab Thickness	100mm
17.	Thickness of brick wall	230mm

TABLE 2
CONSIDERED EARTHQUAKES FOR NTHA

S.No.	Earthquake	Country	Date	Station	Hypocenter
1	Chi Chi	Taiwan	25 Sept, 1999	Tcu080	10.2 Km
2	Kobe	Japan	16 Jan, 1995	KJMA	1.0 Km
3	El Centro	USA	19 May, 1940	USGS Stn. 0117	12.2 km
4	Loma Prieta	USA	18 Oct, 1989	CSMIP Stn. 1667	65.2 Km
5	North Ridge	USA	17 Jan, 1994	CSMIP Stn. 24514	9.9 Km

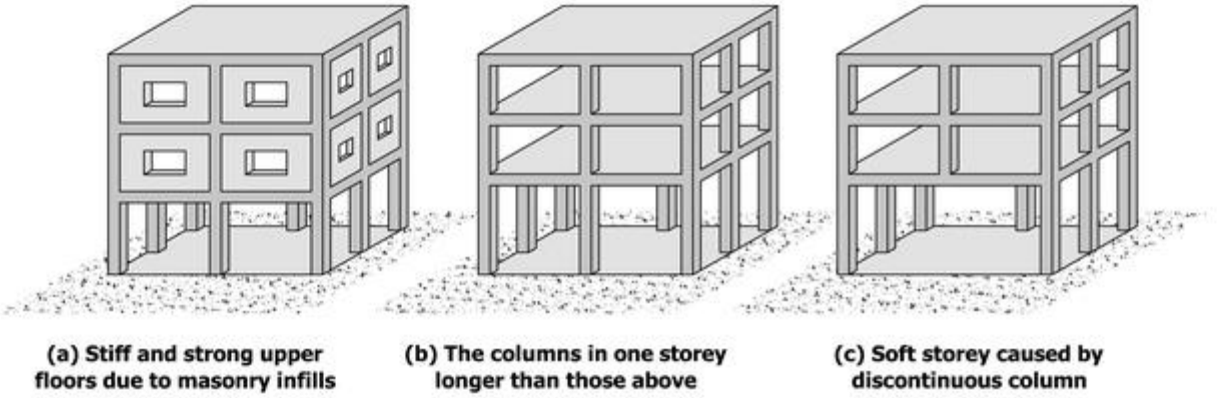
(a) Stiff and strong upper floors due to masonry infills
(b) The columns in one storey longer than those above
(c) Soft storey caused by discontinuous column

FIGURE 1: Examples of soft storey configurations

TABLE 3
SCALING OF GROUND MOTIONS (Target PGA of Zone V = 0.36 g)

S.No.	Earthquake	PGA (cm/s2)	Target PGA (cm/s2)	Scale Factor
1.	Chi Chi	527.23	353.16	0.669
2.	Kobe	805.45	353.16	0.438
3.	El Centro	341.61	353.16	1.033
4.	Loma Prieta	281.40	353.16	1.255
5.	North Ridge	826.80	353.16	0.427

TABLE 4
SPECTRAL MATCHING DETAILS AS PER 'SEISMO MATCH 2016

S No.	Earthquake	Average Misfit	Maximum Misfit	Maximum Acceleration
1.	Chi Chi	5.1 %	23.9 %	0.973 g
2.	El Centro	4.3 %	29.2 %	1.128 g
3.	Kobe	4.4 %	28.1 %	0.963 g
4.	Loma Prieta	6.5 %	21.0 %	1.084 g
5.	Northridge	3.0 %	22.8 %	1.110 g

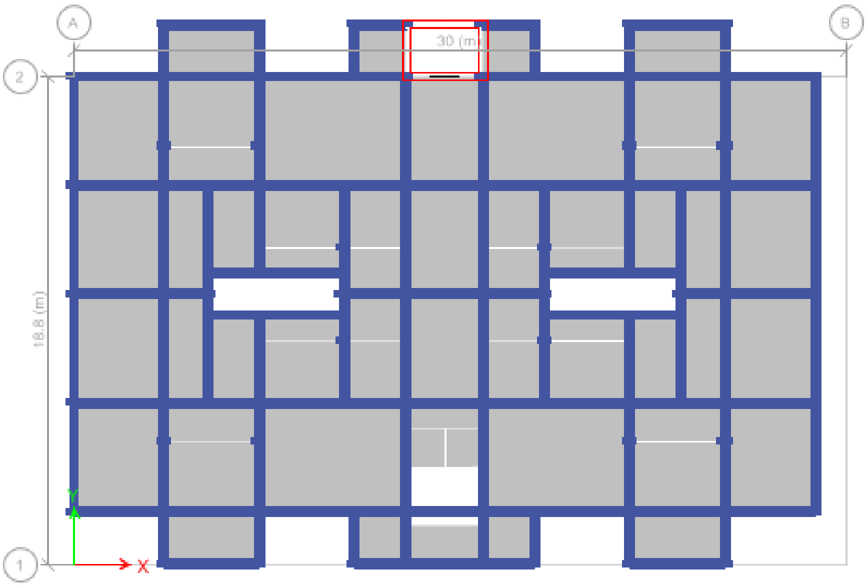

FIGURE 2: Plan of Building (ETABS)

FIGURE 3: Plan of Building (AutoCAD)

TABLE 6

OBSERVED BASE SHEAR FOR DIFFERENT MODELS.

EARTHQUAKES	BASE MODEL (KN)	CROSS BRACED MODEL (KN)	SHEAR WALL MODEL (KN)
Chi Chi	33679.8723	34043.7666	53318.8695
Kobe	40733.5333	41976.6685	56428.338
Loma Prieta	40416.8928	45461.8157	54986.9339
North Ridge	40386.7033	39459.3208	41646.0861
El Centro	40684.9721	44008.9444	54986.9339

3.1 Performance Points:

TABLE 7

PERFORMANCE POINTS OF DIFFERENT MODELS

Model	A – IO	IO- LS	LS-CP	CP-C	C - D	D - E	>E	TOTAL
Base Model	5204	12	5	15	0	0	0	5236
Cross Braced Model	5215	2	19	0	0	0	0	5236
Shear Wall Model	4564	0	0	0	0	0	0	4564

3.2 Storey Drift

A graph is plotted taking floor levels as ordinate and story drifts as abscissa for different models to compare storey drifts.

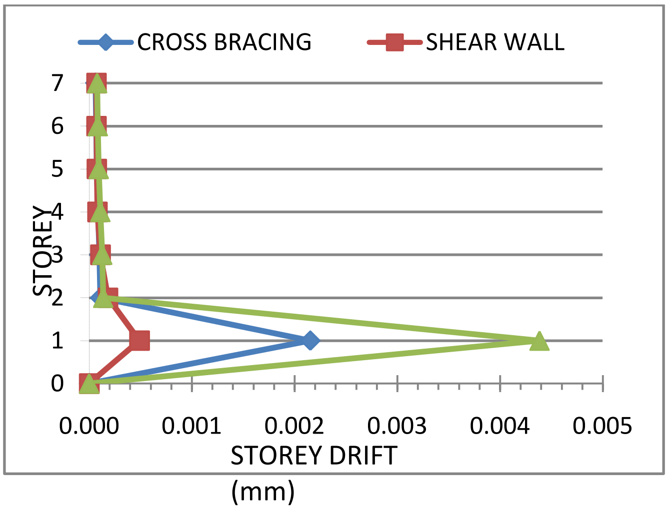

FIGURE 6.1- Observed values of Storey Drifts for Chi Chi

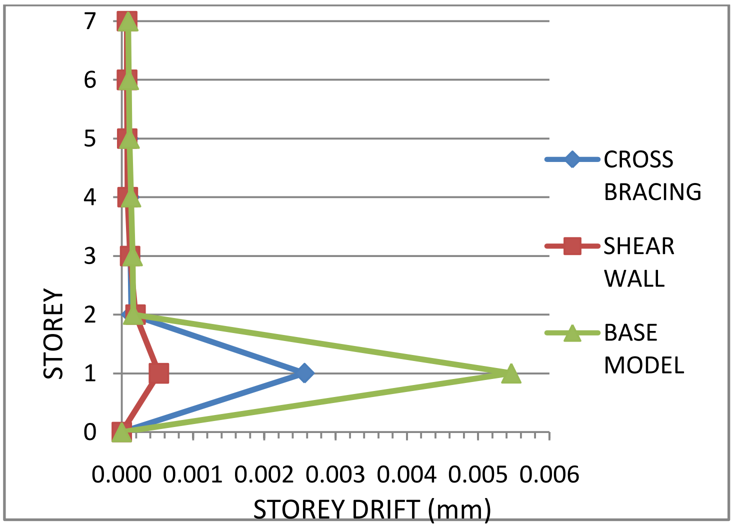

FIGURE 6.2- Observed values of Storey Drifts forkobe

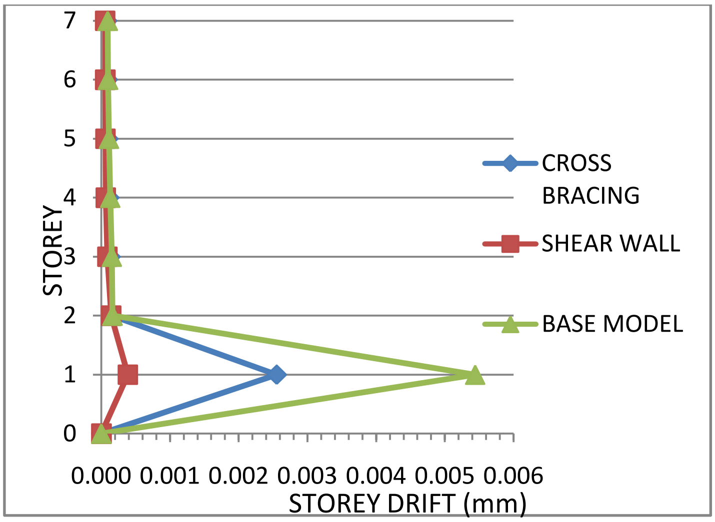

FIGURE 6.3- Observed values of Storey Drifts for El Centro

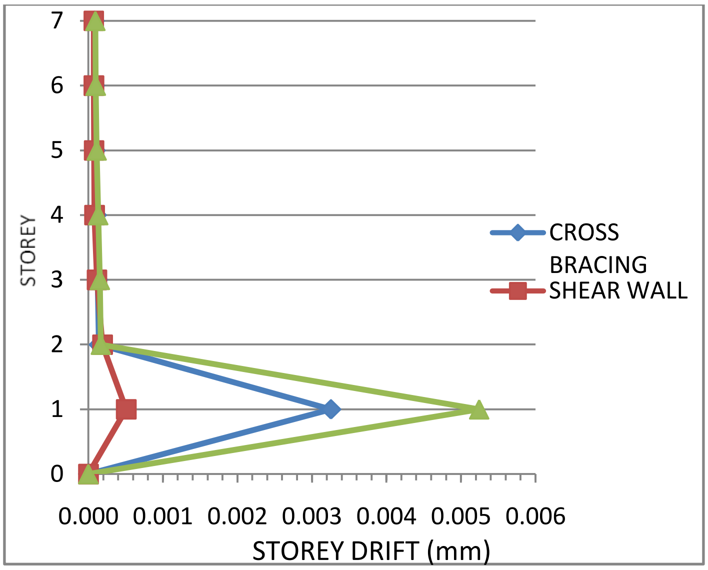

FIGURE 6.4- Observed values of Storey Drifts for Loma Prieta

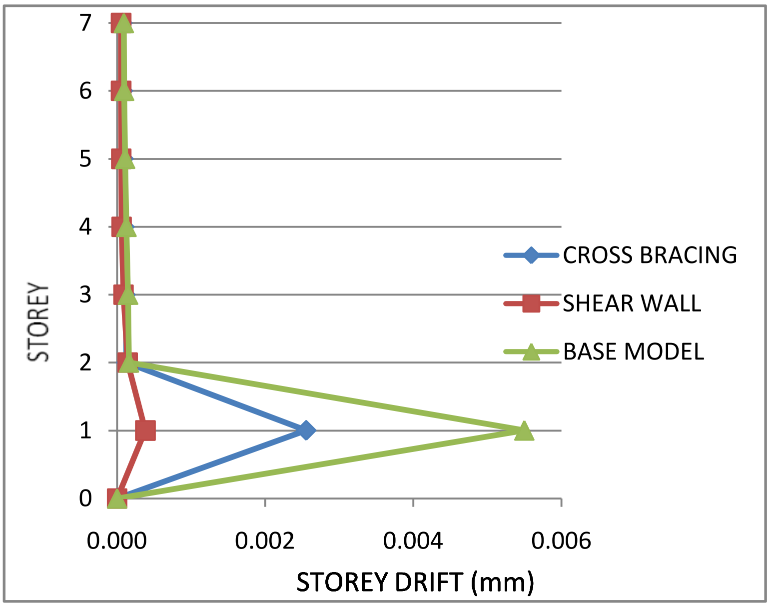

FIGURE 6.5- Observed values of Storey Drifts for North Ridge

From the above profiles it is observed that storey drift in Model I is higher than other two models and it is lesser in Model II. The abrupt change of slope of drift in first storey can be seen in graphs. That means the ductility demand for Model I is largest (27). However the storey drift curve become smoother in Model II that means large stiffness and less ductility demand(27).

3.3 Storey Displacements

A graph is plotted taking floor levels as ordinate and story displacements as abscissa for different models to compare storey displacements.

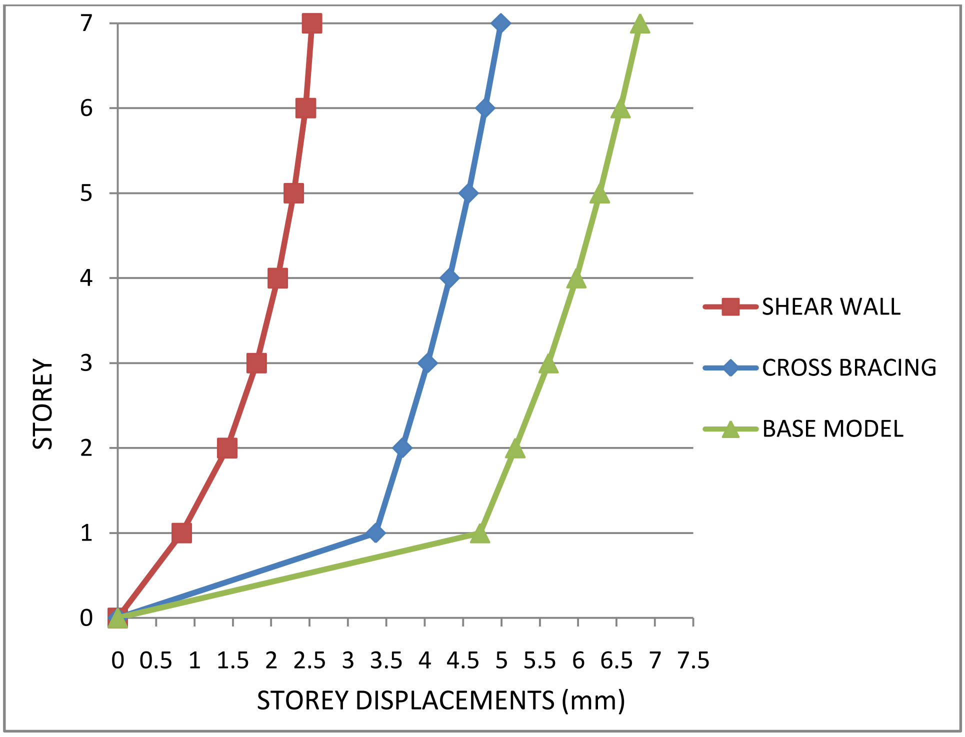

FIGURE 6.6: Observed values of Storey Displacements for Chi Chi

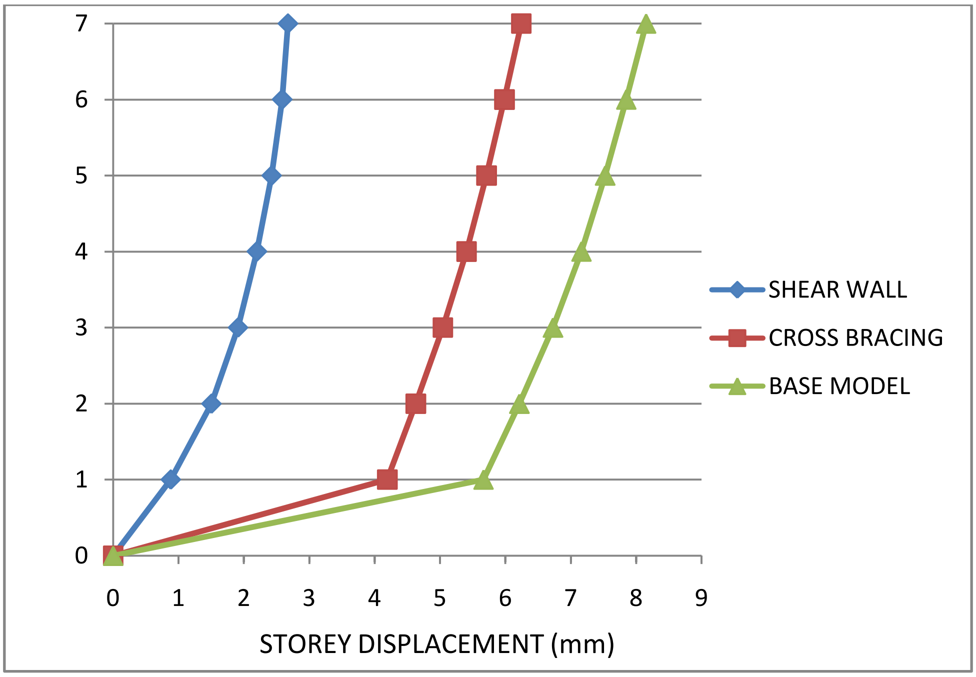

FIGURE 6.7- Observed values of Storey Displacements for Kobe

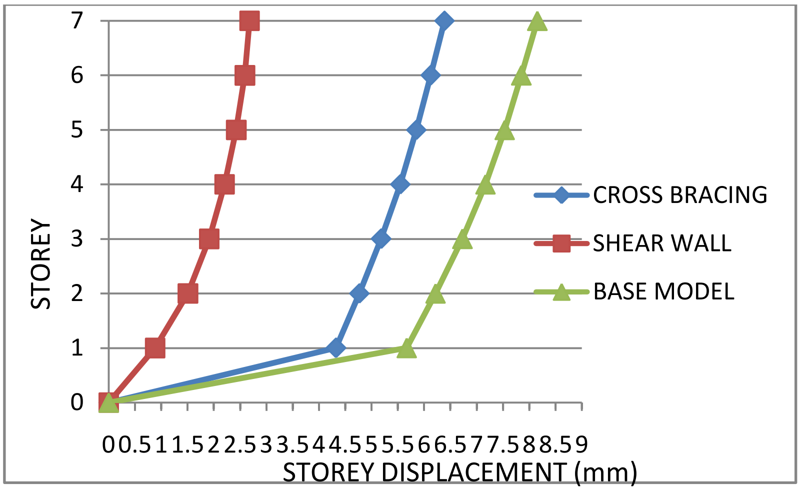

FIGURE 6.8- Observed values of Storey Displacements for El Centro

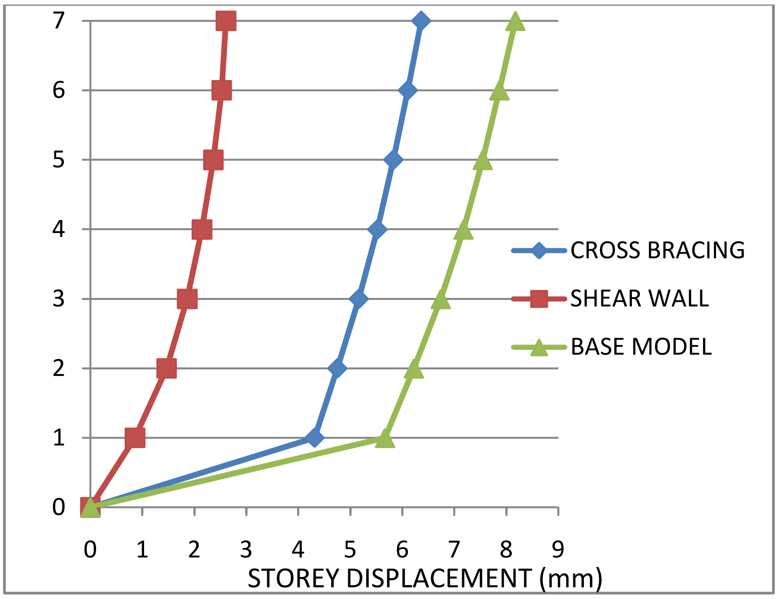

FIGURE 6.9- Observed values of Storey Displacements for Loma Preita

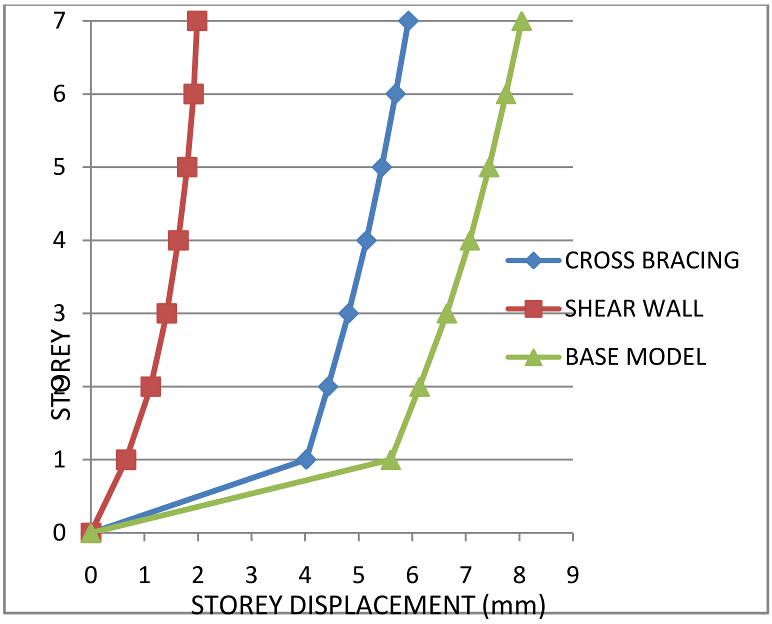

FIGURE 6.10: Observed values of Storey Displacements for North Ridge

From the above graphs it is clearly shown that the large storey displacement in case of soft storey in Model I. On the other hand if shear walls are used in the entire storey (Model II) the displacement is very small as compare to other two models. If we use shear wall in the structure then it reduces 75% displacement whereas if the cross bracings are used in the soft storey of base model then it will reduce 26% displacement.

3.4 Time Period

A graph is plotted taking modes as Yaxis and time period in X axis for all the models shown in figure below-

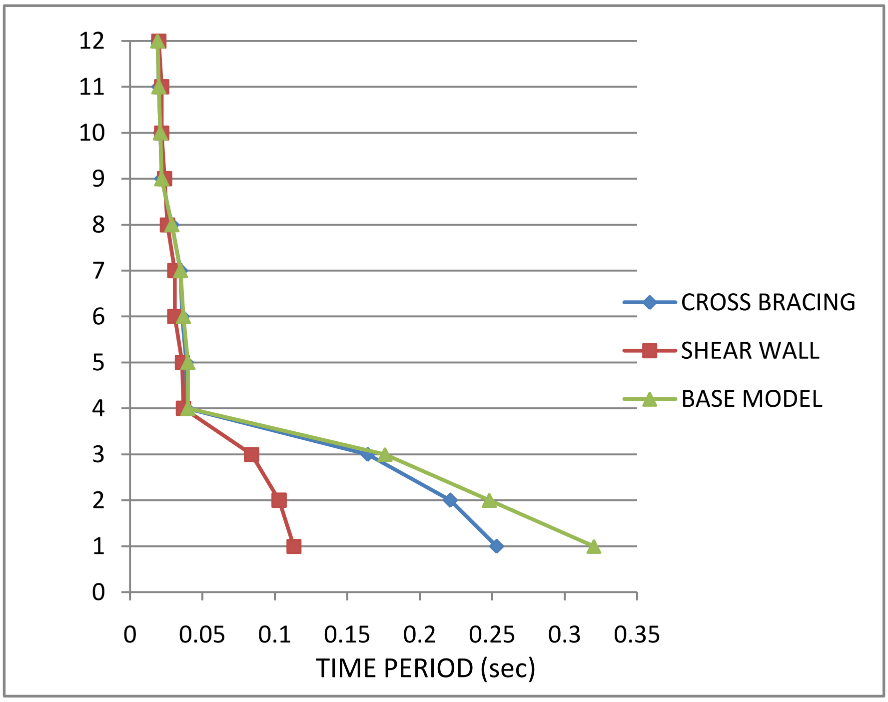

FIGURE 6.11: Comparison of time period for different modes in zone V

It is observed that the time period of vibrations for all the three models it is considerably reduced for models II and III as compared to model I. The model II having shear wall reduces time period in large extent as compare to model I and III which is base model and retrofitted with cross bracing respectively.

3.5 Base Shear

The base shear of different models are mentioned below-

TABLE 6
OBSERVED BASE SHEAR FOR DIFFERENT MODELS.

EARTHQUAKES	BASE MODEL (KN)	CROSS BRACED MODEL (KN)	SHEAR WALL MODEL (KN)
Chi Chi	33679.8723	34043.7666	53318.8695
Kobe	40733.5333	41976.6685	56428.338
Loma Prieta	40416.8928	45461.8157	54986.9339
North Ridge	40386.7033	39459.3208	41646.0861
El Centro	40684.9721	44008.9444	54986.9339

Shear induced at the base of building during earthquake is called base shear which depends on the seismic mass and stiffness of building. Variation in base shear is as shown in table 3(a) and 3(b). It is observed that due to consideration of infill base shear has increased. Among all the different models, the building having shear wall i.e. model II has maximum base shear. Higher the base shear higher is the rigidity of the frame and more is the rigidity lesser is the displacement which can be seen in displacement graphs.(1)

3.6 Performance Points

TABLE 7
PERFORMANCE POINTS OF DIFFERENT MODELS

Model	A – IO	IO- LS	LS-CP	CP-C	C - D	D - E	>E	TOTAL
Base Model	5204	12	5	15	0	0	0	5236
Cross Braced Model	5215	2	19	0	0	0	0	5236
Shear Wall Model	4564	0	0	0	0	0	0	4564

The plastic hinges may be applied to the beams, columns and bracings to study the nonlinear behavior as they show the structural conditions at different stages. Hinges will attain a collapsible condition after passing through some intermediate stages i.e. immediate occupancy (IO) and life safety (LS) levels. The formation of maximum number of hinges in the early stage is not good for the structure as it signifies the early reaching of collapse of the structure. From Table , it is clear that the number of hinge formation in retrofitted building by shear wall is less compared to the base model and retrofitted bycross bracing, thereby making it safer.

3.7 Capacity Spectrum Curve

In the graph shown below the retrofitted model with shear wall will have a higher performance level owing to the lower spectral displacement. This performance level can be found by overlapping the capacity spectrum with the Sa vs. Sd curve of target spectrum where Sa stands for spectral acceleration and Sd stands for spectral displacement.

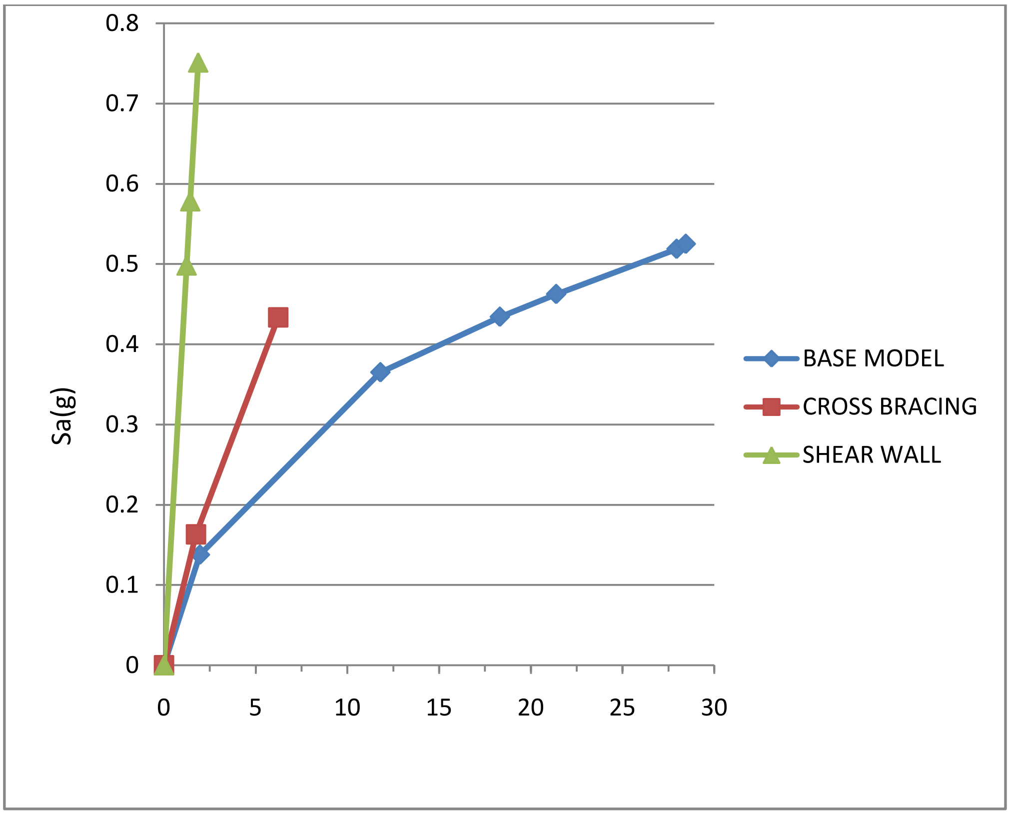

FIGURE 6.12: Capacity Spectrum

The ability of a structure to undergo inelastic deformation beyond the initial yield deformation is termed as ductility displacement. The ductility displacement demand of a given earthquake load is obtained from the pushover curve. The more the ductility displacement the more ductile is the structure. It can be clearly seen that the retrofitted building with shear wall has lesser ductility displacement.

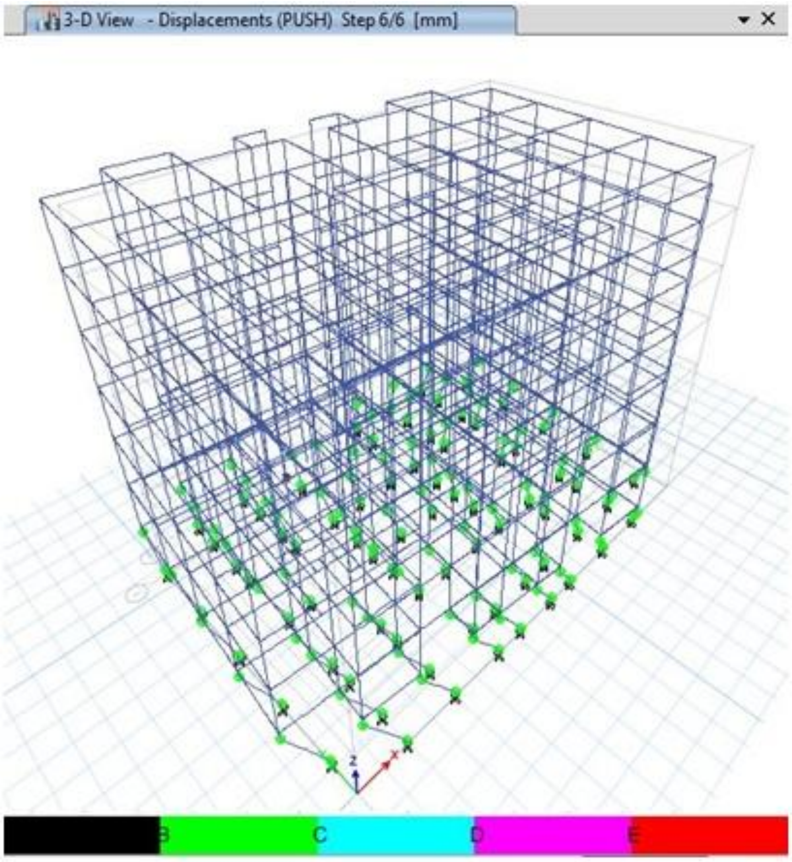

FIGURE 6.13: Hinge failure pattern for base model

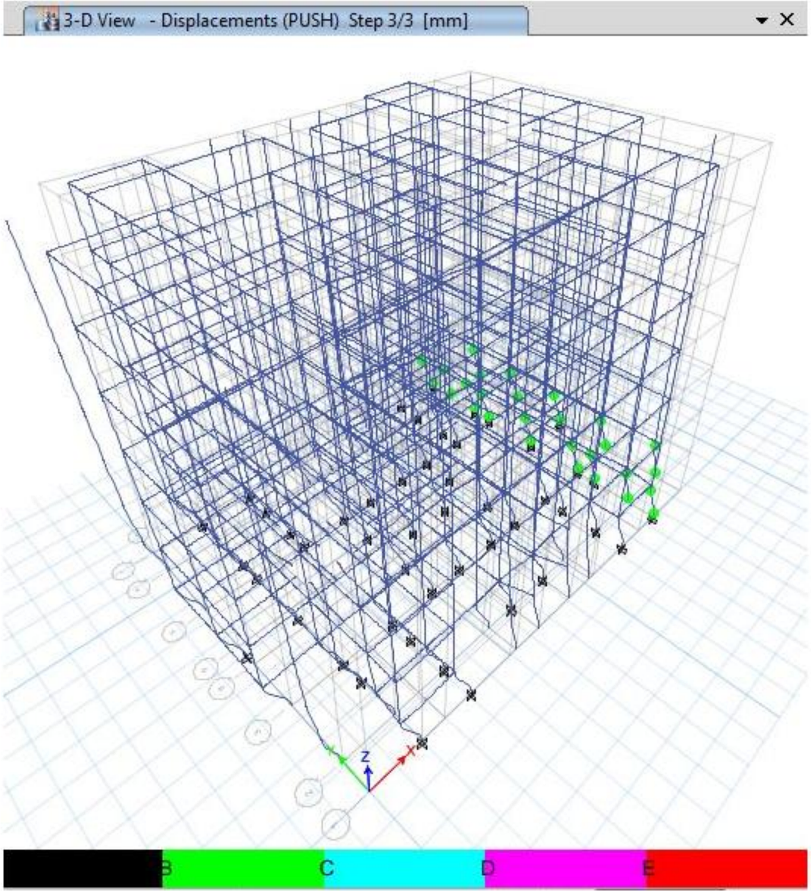

FIGURE 6.14: Hinge failure pattern for model retrofitted by shear wall

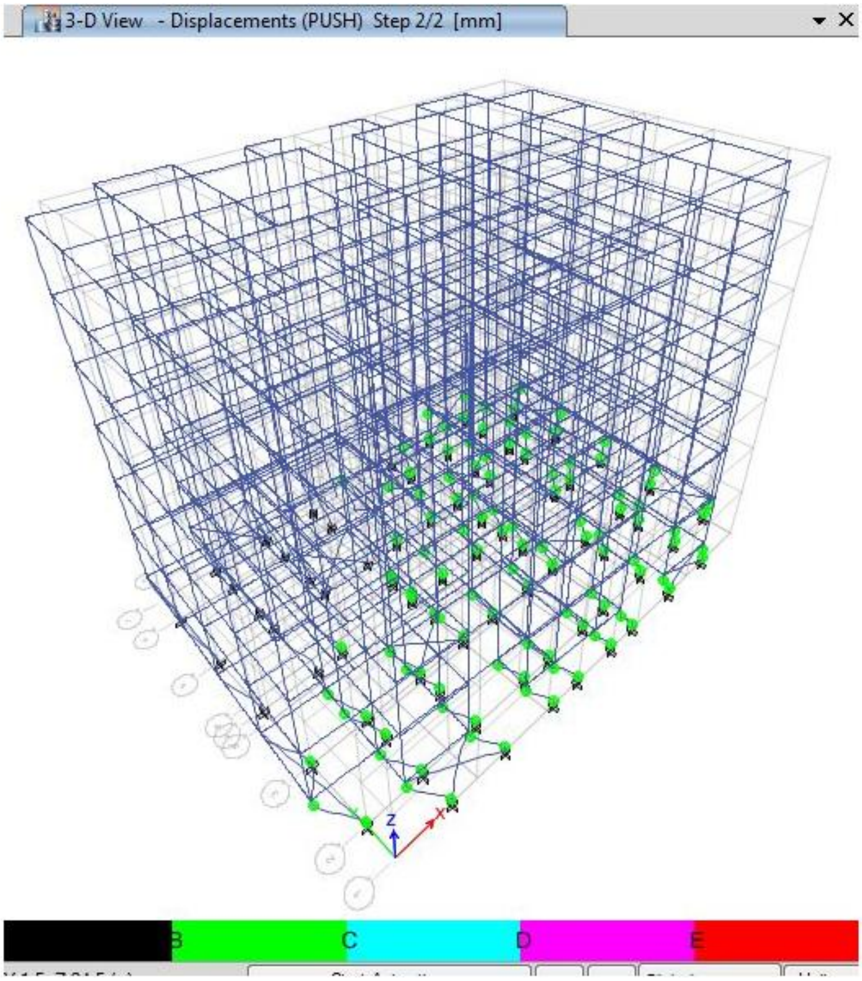

FIGURE 6.15: Hinge failure pattern for model retrofitted by cross bracing

IV. CONCLUSION

The nonlinear behavior of the structure taken as case study of Zone V (Guwahati) had been analyzed for Time History as well as Pushover Analysis. It was subjected to a suite of six different earthquakes which were scaled as per the target spectrum of Zone-V and the performance of the structure was evaluated. The storey drift, storey displacement, base shear, time period, performance points and capacity spectrum have been observed and evaluated for base model and retrofitted with shear wall and cross bracings (both in different models). The behavior of retrofitted structure with shear wall may be significantly different from what has been observed for base model and cross bracing retrofitted structure. Synthesis of the observed seismic response has led down to the following conclusions-

1. Storey drift is reduced in base model due to introduction of shear wall as compared to cross bracing in great extent.
2. Storey displacement is reduced by 75 to 80% in model II and 23 to 26% in model III as compared to model I.
3. The time period of vibrations for all the three models was analyzed. It is considerably reduced for models II and model III as compared to model I.
4. Base Shear of models were analyzed and it is clearly shown that the base shear of the structure heavily increases and makes the structure more stable against seismic action by using shear wall for retrofitting of the structure.
5. The pushover analysis highlights the performance points in different models. It is shown that the performance of base model is poor as compare to other two models. After retrofitting the base model with shear wall the hinges are not formed beyond immediate occupancy level which makes structure safer.
6. In capacity spectrum curve model II shows less ductility demand under higher acceleration.

A financial feasibility study was also carried out, taking in to consideration the cost-benefit ratio, and it can be concluded that shear wall is an effective technique of retrofitting the structure against lateral loadings.

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A Review on Need of Adopting Renewable Energy in India

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Abstract— *India became the world 3rd largest producer and 3rd largest consumer of electricity. The rapid increase in energy consumption in the present scenario and is moving fast towards the development of civilization.[1] Today we are dependent on fossil fuels to power our homes and to fuel our vehicles and mostly we are using the fossil fuels as a primarily heating medium. The huge consumption of fossil fuels has caused a severe damage to our environment and also these resources are limited and expensive but we are only seeing our convenience as we all know it very easy to use coal, oil & natural gas for meeting our requirements. To meet the crisis of energy in India it has been experienced to renewable sources like wind energy, geothermal energy, solar energy, tidal energy, bio-gas energy, etc. In this paper we have initiated to study about the renewable energy resources of the country. [4] In this research paper we have identified the utilization of renewable sources and their benefits to prevent our environment from the pollution created by the fossil fuels.*

Keywords— Energy crisis, Fossil Fuels, Geothermal energy, Solar energy, Tidal energy, Wind energy.

I. INTRODUCTION

In this era of competitiveness every country of this world wants to be in the forefront of developed countries by their intensive growth and generation of employment in its country. Due to the ecological disequilibrium caused by the rapid growth in industrial sector and also due to the growth in population the demand of energy has been increased which we can't be unhide & that results in the emission of immense amount of carbon. For a vast and highly populated country like India. We stand 6th in the entire world in phase of energy consumption & the dependency on single resources to meet the energy requirement of all the country is not a good idea. So India has to incorporate a non-carbon emitting resource which has became an integral part to maintain continuality and to decrease the burden on fossil fuels reserves. Also due to the huge consumption of fossil fuels it has created a lot of environment problems and which disturbs our ecological cycle.[3] So now its high time and we all have to focus on the generation of clean energy and the renewable energy has an potential for fulfilling the energy requirement of India but it is totally dependent on the effective generation and consumption of energy. In the present scenario Indian govt. is giving their full support to the renewable energy generation and soon we will be the work leader in terms of promoting and using of renewable energy. India is the largest consumer of fossil fuels like coal, petroleum, oil etc. This unmanageable growth in the usage of non-renewable energies like fossil fuels, natural gas, oil etc. has been led to an variation of demands & supplies of these fuels.[6] This will affect the uncertainty of future scope of non-renewable energies and this will results the nation to acquire the energy from other countries to attain the need of our country. So we have to adopt the culture of using renewable energy resources so that we can accelerate the enlargement of our energy sector in country and we can meet our requirements.

II. RENEWABLE ENERGY RESOURCES IN INDIA

2.1 Hydropower

Hydropower is the most reliable and largest source of renewable power producing about 13.5 percent of the nation's electricity. India is the 7th largest producer of hydro electric power in the entire world. India hydroelectric power potential is estimated near about 1,48,700 MW. The hydro power plants basically convert the energy of flowing water into electricity. Basically kinetic energy of water is being converted to electrical energy. The most common sort of generating the electricity from hydro powerhouse uses a dam on a river to retain an outsized reservoir of water.[2] Water is than released through turbines in order that power are often generated.

However hydropower plants does not produce no air emissions but can affect the water quality and wildlife habitats. Therefore the designing of hydropower plants is now being changed so that we can minimize the impacts on the rivers. Some of the power plants are diverting some of the flow around their dams to imitate the natural flow. But while this we can improves the wildlife river habitat, but at the same time it reduces the power plant output. The hydro power plant are preferred to those place where there is heavy rainfall present such places are- Andhra Pradesh, Himachal Pradesh, Madhya Pradesh, Uttarakhand, Jammu & Kashmir, Maharashtra etc.[5][6]

2.2 Solar Power

Solar power in India is the fast developing industry. The country solar installed energy has been reached upto 34.404 GW till 29 feb 2020. The Indian government had an initial target of 20 GW capacities for 2022 which was achieved four years ahead of scheduled time period. In 2015 the target was raised to 100 GW of solar capacity by 2022, which also includes the 40GW of Roof top solar power plants, & targeting an investment of US$100 billion. India has established nearly 42 solar parks to create land available to the promoters of solar plants.[7]

India expanded its solar-generation capacity 8 times from 2,650 MW on 26 May 2014 to over 20 GW as on 31 January 2018. The country added 3 GW of solar capacity in 2015–2016, 5 GW in 2016–2017 and over 10 GW in 2017–2018, with the common current price of solar electricity dropping to 18% below the common price of its coal-fired counterpart. By the tip of September 2019 India has installed quite 82,580 MW of renewable energy capacity with around 31,150 MW of capacity under various stages of installation. The main working of generating the solar power is that the heat energy which is released from the sun is being converted into electrical energy with the help of solar panels and then it will be transmitted to grid.[8]

The alternative energy is extremely beneficial for us as India is being situated between the tropic of cancer and therefore the equator, and having a median temperature of 25 degree Celsius – 27.5 degree Celsius and receives 260-300 clear sunny days each year. Major solar plants are located in Gujarat, Rajasthan, Orissa, Tamil Nadu.

2.3 Wind Energy

Wind energy is the most beneficial form of generating energies. From wind energy we can generate two forms of energies.

1. Electrical Energy
2. Mechanical Energy

Wind power generation capacity in India has significantly increased in recent years. As of 31st December 2019 the entire installed wind generation capacity of India was 37.505 GW, which is that the fourth largest installed wind generation capacity within the world. Wind generation capacity is especially spread across the Northern, Southern and Western regions.

Wind power costs in India are decreasing rapidly. The levelized tariff of wind generation reached a record low of ₹2.43 (3.4¢ US) per kWh, (without any direct or indirect subsidies) during auctions for wind projects in December 2017. Wind generation accounts for nearly 10% of India's total installed power generation capacity and generated 62.03 TWh within the twelvemonth 2018-19, which is sort of 4% of total electricity generation.[6]

2.4 Biomass Energy

Biomass energy is additionally referred to as Bio Energy. Bio energy means (Organic matter) like plants. If you have got burned wood in fire place or campfire you have got used bio energy. But we don’t get all of our biomass resources from tress or the opposite plants. One third contributor of energy to India is biomass with a possible 80,467 MW. Which comprises of solid biomass, which is an organic & non fossil material of biological origins? Biogas is nothing but the assembly of methane and greenhouse emission with the assistance of anaerobic digestion of bio mass and then combusted to supply heat. After hydropower biomass is that the leading resource of renewable energy. As some utilities and power generating companies with coal powerhouse have found that replacing some coal with biomass may be a low cost choice to reduce unwanted emissions.

Also we can convert the biomass energy into gas with the help of a simple process called gasification. This gas can burned and used in gas turbine and which is another way of generating electricity. [1]

Biomass may be converted directly in to liquid fuels which are generally called as biofuels. As India is principally that specialize in producing biofuels, because biofuels are easy to move and possess high energy density. The foremost common biofuel is ethanol, an alcohol made of the fermentation of biomass which is high in carbohydrates. This largest source of ethanol is corn which we also called as sugarcane.

Another biofuel is biodiesel which might be made of vegetable and animal fats. Biodiesel will be wont to fuel the vehicles or as a fuel addictive to manage the emissions.

2.5 Geothermal Energy

Geothermal energy is that the heat from the world and it's a clean and sustainable. Heat is incredibly much cost effective and an environmental friendly thermal energy generated and stored inside the world surface. This can be an only energy resource that has not been exploited in any respect which is an unlimited power resource that's clean, reliable and residential grown. We are totally captivated with the usage of coal and due this our environmental conditions are becoming worst & India soon will should start exploring this source of energy. Because the heat has an potential of about 10,000 MW. Resources of heat range from the shallow ground to predicament and hot rock found some miles below the earth's surface and also are also down even deeper to the extremely high temperatures of molten rock called magma. This process takes place because of the slow decay of radioactive particles, the warm temperature produced inside the world and it happens inside all the rocks. Heat is thermal energy which is generated through the natural hot springs.

In India, by the time heat installed capacity is experimental; however the potential capacity is quite 10,000 MW.

Following are the six most promising heat power plants in India −

1. Tattapani in Chhattisgarh.
2. Puga in Jammu & Kashmir.
3. Cambay Graben in Gujarat.
4. Manikaran in Himachal Pradesh.
5. Surajkund in Jharkhand.
6. Chhumathang in Jammu & Kashmir

Corn ethanol and bio diesel provide only about 0.4% of total liquid fuels market. to increase our available supply of biofuels, researchers are testing crop residues like cornstalks and leaves, wood chips, waste food, & even trash as potential biofuel sources..

2.6 Nuclear Energy

Nuclear power is that the fifth largest source after the coal, hydro, gas & wind energy. As of march 2018 India has 22 nuclear reactors operational fewer than 7 atomic energy plants having the overall capacity of 6,780 MW. Atomic energy produced a complete of 35 TWH and supplied 3.22% of Indian electricity in 2017. 7 more reactors are under construction with a combined generation capacity of 4300 MW.

India's domestic uranium reserves are small and also the country relies on uranium imports to fuel its atomic energy industry.[6] As within the early 1990s Russia has been the foremost supplier of the fuel to India. Thanks to the shrinking in domestic uranium reserves, electricity generation from atomic energy plants in India has been declined to 12.83% from 2006 to 2008. After a waiver from the nuclear supplier group. (NSG) in September 2008 which allowed to commerce the international nuclear trade. India has also signed the bilateral deals on civilian energy technology cooperation with several other countries including France, u. s., the uk, Canada & Asian country. India has also an uranium supplying agreement with Russia. Also an Indian private company has won a uranium exploration go for niger. The working of nuclear energy plant is sort of interesting and is that the fastest way of generating a bulk amount of electricity.

As within the nuclear energy plant neutrons hit uranium atoms, splitting them. This split releases neutrons from the uranium that successively hit other atoms, causing a series reaction. This chain reaction is controlled with "control rods" that absorb neutrons. Within the core of nuclear reactors, the fission of uranium atoms releases energy that heats water to about 520 degrees Fahrenheit. This quandary is then accustomed spin turbines that are connected to generators, producing electricity.

2.7 Ocean Energy

There is an enormous potential of tidal and marine energy in India which might be produced from ocean. India features a long coastline of 7517 km which is marked along by numerous estuaries and gulfs which makes it more attractive for the event of marine energy projects. India's total wave potential is near about 40GW – 60 GW.

However compared with the developments in other renewable energy technologies, ocean energy technology like wave and tidal are in their nascent stage of development in India. Wave power depends upon the peak of the wave and its period. Primary estimates of wave energy potential along Indian coast is around 5-15 MW/m, therefore the theoretical estimated potential comes intent on be around 40-60 GW.[2] A study by IIT Madras and Credit Rating Information Services of Indian Ltd (CRISIL) have shown that western coast has higher wind generation potential compared to eastern coast.[3] they need identified potential locations for wave power development along the geographical region of India in Maharashtra, Goa, Karnataka and Kerala. Kanyakumari located at the southern tip of Indian peninsula has the very best power thanks to the results of refraction and powerful winds.[3] With currently available technologies, amount of power that may be generated using wave energy is way but the theoretical estimated potential.

Capacity Utilization factor for wave energy in India is within the range of 15-20%. For the tidal energy potential the most effective locations are the Gulf of Cambay and therefore the Gulf of Kachchh on the geographical region having the utmost tidal range of 8m-11m and having the common range of 5m to 7m. The Ganges Delta, Sunder Bans province is good for locating small scale tidal power plants. The tidal power potential in India is 8000-9000 MW within the gulf of cambay, 1200 MW within the gulf of Kachchh & but 100 MW within the sunder bans.

III. REASONS FOR ADOPTING RENEWABLE ENERGY INSTEAD OF NON-RENEWABLE ENERGY

There are many reasons for adopting the culture of using renewable energy resources over the Non-Renewable energy resources. The explanations are listed below:-

- Renewable energy resources are ample in nature at free of cost while Non- renewable energy resources are restricted in nature and also they are present in nature in free of cost.
- There is no adverse effect of renewable source on environment but Non renewable energy sources creates a lot of pollution and is very harmful for our environment.
- A renewable source does not release any harmful gases in the environment while the other one emits the greenhouse gases in our environment.
- Renewable energy technologies use resources straight from the environment to come up with power. These energy sources include sunshine, wind, tides, and biomass, to call a number of the more popular options. Renewable resources won't run out, which cannot be said for several kinds of fuels – as we use fossil fuel resources, they'll be increasingly difficult to get, likely driving up both the price and environmental impact of extraction.
- The Non-renewable energies are not provided free of cost and also they are not distributed evenly in the world while the renewable resources are present in the nature in free of cost and also they are evenly distributed in the whole world.
- Renewable energy technologies required less maintenance rather than the non- renewable energy technology as they don't have any moving parts and also they don't rely on flammable, combustible fuel sources to operate.

- Renewable energy helps all people to save lots of money for the long run not only in maintenance but also on our budget items as they doesn't required to pay the number for the fuel.

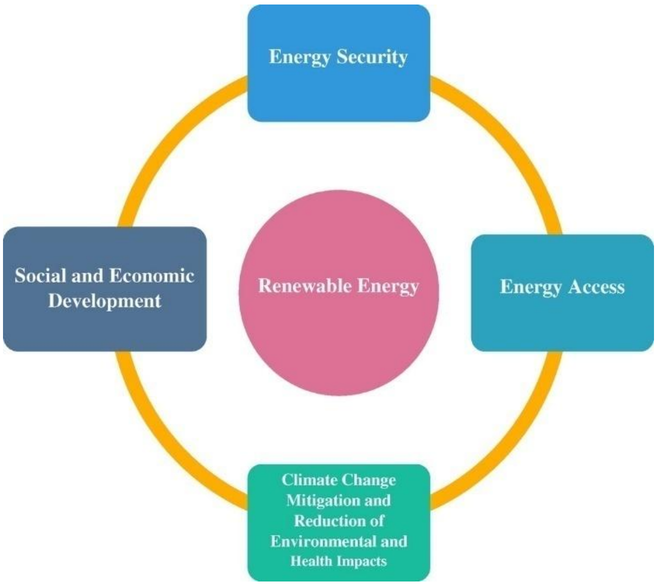
IV. ASSESSMENT OF RENEWABLE ENERGY BASED OF DIFFERENT CATEGORIES

TABLE 1
OVERALL ASSESSMENT OF RENEWABLE ENERGY OF INDIA

Category	Hydro	Solar	Wind	Biomass	Geothermal	Nuclear	Ocean
Efficiency (%)	85-90	15	35-45	20-25	10	33-37	3
Approx. Potential of India	148700	0	375050	80467	10000	0	49000
Area Requirement	Very High	High	High	Extremely High	Low	Very Low	Very Low
Categories	Hydro	Solar	Wind	Biomass	Geothermal	Nuclear	Ocean
Installed Capacity (MW)	45399	29549	36368	9806	0	6780	1
Cost	Very High	Low	Low	Low	High	Low	High
Risk	High	Low	Low	Low	Low	Very High	Low
Construction Time	Vey High	Less	Less	Average	High	High	High
Waste Generation	Nil	Nil	Nil	Some waste	Nil	Toxic Gases	Nil
Operation & management costs	Low	Very Low	Very Low	Very Low	Low	High	Moderate
Carbon Di Oxide (kgco2/kwh)	0.04	0.1	0.02	1.18	0.06	0.025	0.02
Energy Sources	Inexhaustible	Inexhaustible	Inexhaustible	Depends on Biomass Availability	Limited But Inexhaustible	Exhaustible	Variable But Inexhaustible

V. RENEWABLE ENERGY AND SUSTAINABLE DEVELOPMENT

We all know that renewable energy encompasses a direct relationship with sustainable development through its effect on the human development and economic productivity. Renewable energy resources provides the opportunities in energy security, social, and economic growth, energy crisis, and reduction in environmental and health effects.[4]



1) **Energy Security: -** the world energy security is usually used however there's no consensus on its precise interpretation. Energy security is predicated on the thought that there's continuous supply of energy. because the renewable energy source are distributed evenly round the globe as compared to fossil fuels and other non- renewable energy resources. The introduction of renewable resources may made contribution to increasing the reliability of energy sources, to be specific in areas which are often suffers from insufficient grid access.

2) **Social And Economic Development:-** Generally the energy sector has been taken as a key to the economic development having a powerful correlation between economic process and expansion of energy conversion. Globally per capita incomes are positively corelated with per capita energy use and economic process will be identified because the most essential factors behind increasing energy consumption. By a general survey in 2008 it's been proved that the use from renewable energy technology was about 2.3 million jobs across the globe wide which is able to also helps in improving health, education, gender, equality and environmental safety.[1]

3) **Energy Access:** The aim of the sustainable development is to confirm that the energy which is generating must be clean, affordable, available and accessible to any or all and this may only be achieved with renewable energy sources, since they're generally distributed across the world. Access concern have to be understood in an exceedingly local context and in most countries there's a difference between the energies within the urban and rural areas. [4]

4) **Climate Change Mitigation And Reduction Of Environmental & Health Impact:-** Renewable energy sources are utilized in energy generation and helps to scale back green house gases which mitigates in change of weather conditions, reduce environmental stress, and health complications which are related to pollutants from fossil fuels. The change in GHG emissions of India for 1980-2015.

   The following policies recommendations emanating from the study that can help to mitigate climate change.

   - All sectors and regions must invest in renewable energy technologies and policies.
   - Reducing carbon foot print through the changes in life style
   - More researches and innovations so that we can reduce the land size and makes the system more efficient.

VI. RESULTS AND FINDINGS

Efficiency of the energy generation process intricate is highest in hydro power which is near about 85%-90% and least in the biomass and ocean energy.

Land requirement for biomass is extremely high in comparison to the other forms of energy however hydro power also needs the large land but less than the biomass.

In terms of installed capacity hydro power has the largest installed capacity in India.

The CO2 generated is simply high for the biomass energy, & all other renewable energy involves the negligible or very less Co2 emissions.

The overall project cost for the hydro & nuclear power plants are very high as they require high capital income to invest initially than the others.

Risk factor is very high in nuclear power plant which includes both the social and individual risk. As the nuclear power plant subjects to health fears due to its risky operation. That's why power generation from nuclear power plants are not been preferred so much in comparison to the wind, solar geothermal, etc.

However hydro power plants need a lot of construction time for installing a power plant. Geothermal, nuclear & ocean power plants are also needs time for construction but less than the hydro power plants. Solar & wind power plants needs a very less time for installation.

Waste generated are nearly negligible altogether the ability plants except the atomic energy where the highly radioactive wastes are produced and that they need a correct waste management plant for settling up the waste.

The operational and management cost is high for the nuclear power plant and these are very low for the solar, wind & biomass. However ocean power plant needs an moderate value of cost.

Energy source for wind, solar, geothermal and ocean are inexhaustible whereas for the biomass & nuclear energy it's exhaustible.

VII. CONCLUSION

After viewing the present scenario od India, it has been cleared that the renewable sources are cost effective, user friendly and can easily beat the fossil fuels. Due to the inconsistency in energy distribution, renewable energy has the capability to became the foundation for fulfilling the country's future energy requirement. As these sources will remove the dependency of using the natural resources like coal, oil, gas etc. However there is also a great crash on the economic development of the country through the use of renewable energy as it can reduce the level of unemployment and give chance for improving our employment status. We all know thanks to our excessive growth within the population we face energy crisis as many parts of India are still surviving without electricity in their areas hence we are able to use the renewable energy as an panacea to the issues. But the growth of renewable energy sector is inhibiting due to the unavailability of capital. Future growth in renewable energy requires new technologies, favorable policies backed by innovative financing schemes. This paper is largely for all the stakeholders & government to require charge and discuss the program that favors renewable energy deployment. The Indian government should increase the financial backing within the sector of renewable energy in several styles of ways which incorporates the funds for demonstration projects. This is often only an summary which might help all people to encourage the utilization of renewable energy in a very more rapid & extensively way for the higher development of the country.

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Synthesis of Thiazoles and 1,3,4-Thiadiazoles Bearing Spectral Studies, Biological Evaluation and Structure Activity relationship

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Abstract— *A novel series of thiazole based-1,3,4-thiadiazoles were designed and prepared via the reaction of the 2-(4-methyl-2-phenylthiazole-5-carbonyl)-N-phenylhydrazinecarbothioamide with the appropriate hydrazonoyl chlorides. The structures of the newly synthesized compounds were established based on spectroscopic evidences and their alternative syntheses. Thirteen new 1,3,4-thiadiazoles have been evaluated for their anticancer activity against liver carcinoma cell line (HepG2). Also, their structure activity relationship (SAR) was studied. The 1,3,4-thiadiazoles* ***12d****,* ***12c,*** ***6g****,****18b****,* ***6c****, and* ***6f****(IC$_{50}$ = 0.82, 0.91, 1.06, 1.25, 1.29 and 1.88 µM, respectively) have promising antitumor activity against liver carcinoma cell line (HepG2).*

Keywords— thiazoles; thiadiazoles; hydrazonoyl chlorides; anticancer activity; structure activity relationship.

I. INTRODUCTION

Cancer is a devastating and most common life-threatening disease representing a major health problem for many decades.The clinical application of chemotherapy still considered as a major compartment in treating cancer, however, is often limited by the severity of the side effects and the development of tumor cell resistance against these cytotoxic agents. Clinical administration of high doses of anticancer drugs to overcome resistance leads to severe toxicities [1]. Therefore, the development of novel effective anticancer drugs and strategies is eagerly being pursued.

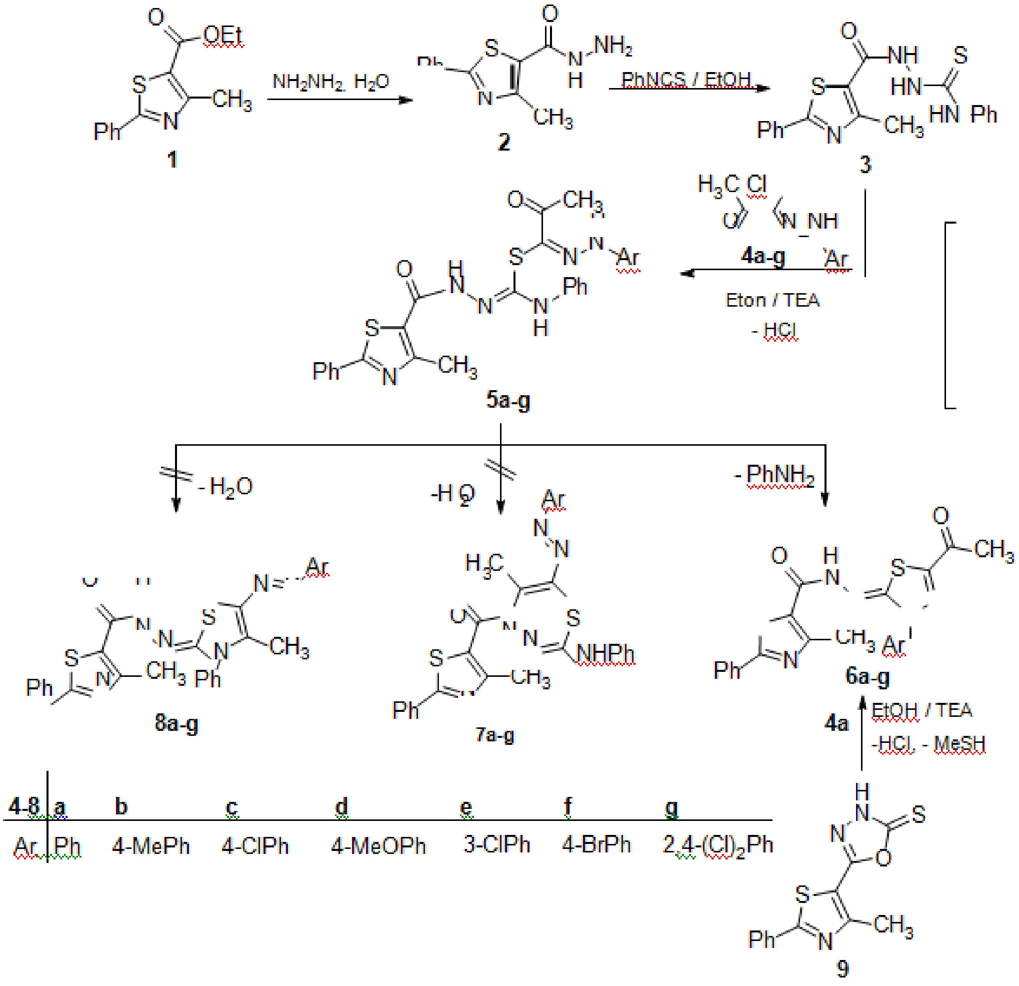
Also, it was reported that Liver cancer is ranked in the top ten human cancers worldwide and among the top five of cancers in terms of mortality [2,3]. A literature survey revealed that a great deal of interest has been focused on the synthesis of functionalized thiazole derivatives due to their synthetic and biological potentialities as antihypertention [4], antifungal [5], antimicrobial [6,7], anti-inflammatory [8], antioxidant [9], antitubercular [10], and anticancer agents [11-14]. 1,3,4-Thiadiazole derivatives have attracted considerable interest due to their wide spectra of biological activities such as antibacterial, antifungal, antituberculosis, antihepatitis B viral, antileishmanial, anti-inflammatory, analgesic, CNS depressant, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic, analgesic, antimicrobial, antitubercular, anticonvulsant and anticancer activities [15–24]. These important biological activities encouraged several research groups to find out different methods for synthesis of new thiadiazoles using different synthones, such as thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, acylhydrazines, and bithioureas [25]. In the light of the above-mentiond findings and in continuation of our efforts to synthesize new bioactive compounds [26-34], this work aims to synthesis a new series of thiazoles and 1,3,4-thiadiazoles bearing thiazole moiety and to study their anticancer activity against Liver carcinoma cell line (HepG2).

II. RESULTS AND DISCUSSION

2.1 Chemistry

2-(4-Methyl-2-phenylthiazole-5-carbonyl)-N-phenylhydrazinecarbothioamide (**3**) was prepared as previously described, via reaction of 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**) with phenyl isothiocyanate in EtOH as depicted in Scheme 1[35].

The presence of the thioamidehydrazine moiety as a side chain in compound **3** prompted us to utilize it for constructing 1,3,4-thiadiazole ring *via* its reaction with hydrazonoyl chlorides. Thus, reaction of compound **3** with the appropriate 2-oxo-*N*'-arylpropanehydrazonoyl chlorides **4a-g** [36] under reflux in ethanol in the presence of triethylamine as a basic catalyst led to formation of the respective 1,3,4-thiadiazoles **6a-g**, rather than thiadiazines **7a-g** or 1,3-thiazoles **8a-g** (Scheme 1). The elemental analysis together with the data derived from IR, ^{1}HNMR and mass spectra are in agreement with the proposed structure **6**. The IR spectra of products **6** showed in each case the presence of two absorption bands around 1700, 1650 cm^{-1} for the two carbonyl groups, in addition to another band near *v* 3350 cm^{-1} for the NH function. The ^{1}HNMR spectra of **6** revealed the presence of broad singlet signals assigned for the NH proton near δ 11.19 ppm, in addition to the expected signals for the protons of the CH_3 group, the acetyl group at position-2 of the 1,3,4-thiadiazole ring and the aryl protons. The mass spectrum of each of products **6** revealed the presence of a molecular ion peak (see experimental section).



4-8	a	b	c	d	e	f	g
Ar	Ph	4-MePh	4-ClPh	4-MeOPh	3-ClPh	4-BrPh	2,4-(Cl)$_2$Ph

SCHEME 1. Synthesis of thiadiazoles 6a-g

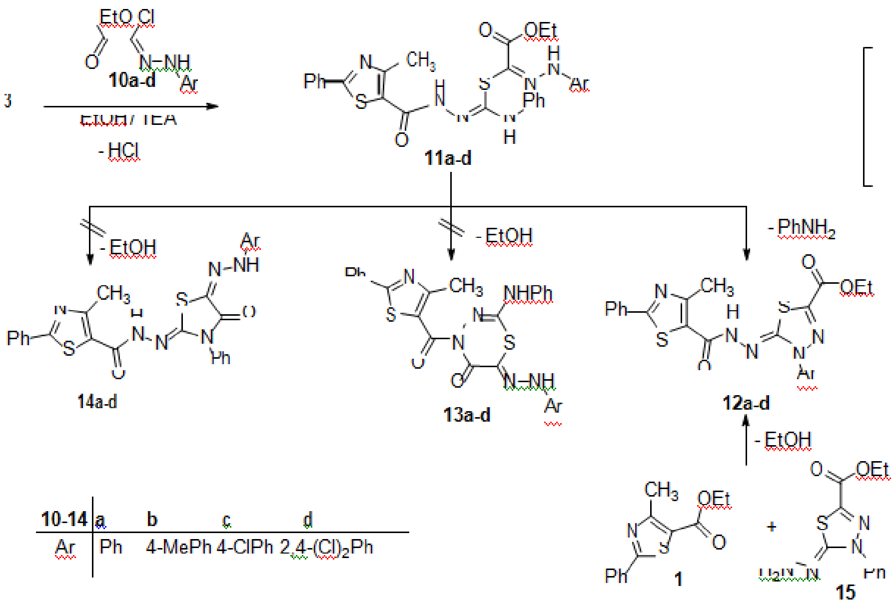
1,3,4-Thiadiazole **6a-g** was assumed to be formed through the intramolecluar cyclization of NH group in the hydrazone moiety with the imino group in the non-isolable intermediates **5a-g,** followed by elimination of aniline molecule to give the respective thiadiazole derivatives **6a-g** (Scheme 1).

The structure of **6** was proved chemically *via* an alternative method (Scheme 1). Thus, the reaction of 5-(4-methyl-2-phenylthiazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione(**9**)[35] with **4a** in ethanol in the presence of triethylamine under reflux led to formation of product which is identical in all respects (mp, mixed mp and IR) with compound **6a**.

Next, in order to test of the biological activities of a vast array of these compounds, we reacted compound **3** with the appropriate hydrazonoyl chlorides **10a-d** [36], under the same experimental conditions, which gave the corresponding 1,3,4-thiadiazole derivatives **12a-d**(Scheme 2).

The IR, and ^{1}H-NMR spectra of **12a** taken as an example of the prepared series, revealed the presence of the ester group and the disappearance of the hydrazone-NH function. Also, the mass spectrum of the reaction products **12a-d** showed, in each case, a peak corresponding to their molecular ions.

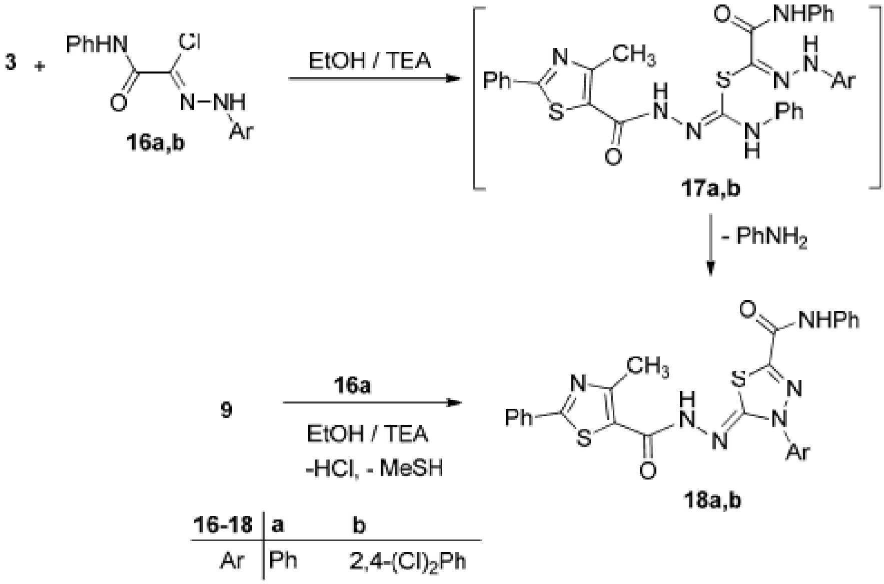
The structure assigned for product **12** was further evidenced *via* an alternative method. Thus, reaction of ethyl 4-methyl-2-phenylthiazole-5-carboxylate (**1**) with 1,3,4-thiadiazole **15** [37] in ethanol under reflux, afforded a product which is typical in all respects (mp, mixed mp and IR) with that obtained from the reaction of **3** with **10a** (Scheme 2). To account for the formation of the product **12**, it was suggested that the reaction of compound **3** with hydrazonoyl chloride **10** initially gave the intermediate **11,** which underwent nucleophilic addition, followed by in *situ* cyclization *via* losing of one molecule of aniline (route a) to give the final product **12.** The other routes (b) and (c) outlined in Scheme 2 were excluded since they led to formation of products **13** and **14**, which were completely different in all respects (IR, ^{1}HNMR, mass spectra) from products **12.**



10-14	a	b	c	d
Ar	Ph	4-MePh	4-ClPh	2,4-(Cl)$_2$Ph

SCHEME 2. Synthesis of thiadiazole derivatives 12a-d

Also, The reaction of compound **3** with hydrazonoyl halide of type **16** was studied. Thus refluxing compound **3** with the hydrazonoyl chloride **16a** or **16b** [36] under the same experimental conditions, afforded the corresponding 1,3,4-thiadiazole derivatives **18a,b** (Scheme 3). The ^{1}HNMR spectrum of compound **18a,** revealed two D$_2$O-exchangeable signals at δ 10.18 and 11.72 corresponding to two NH protons, in addition to an aromatic multiple in the region 7.02-7.78 ppm. Also, its mass spectrum of revealed a molecular ion peak at *m/z* = 512 which is in complete agreement with the proposed structure (see Experimental). In addition, compound **18a** was proved chemically *via* an alternative method from the reaction of compound **9** with **16a** which gave a product identical in all respects (mp, mixed mp and IR) with compound **18a**.



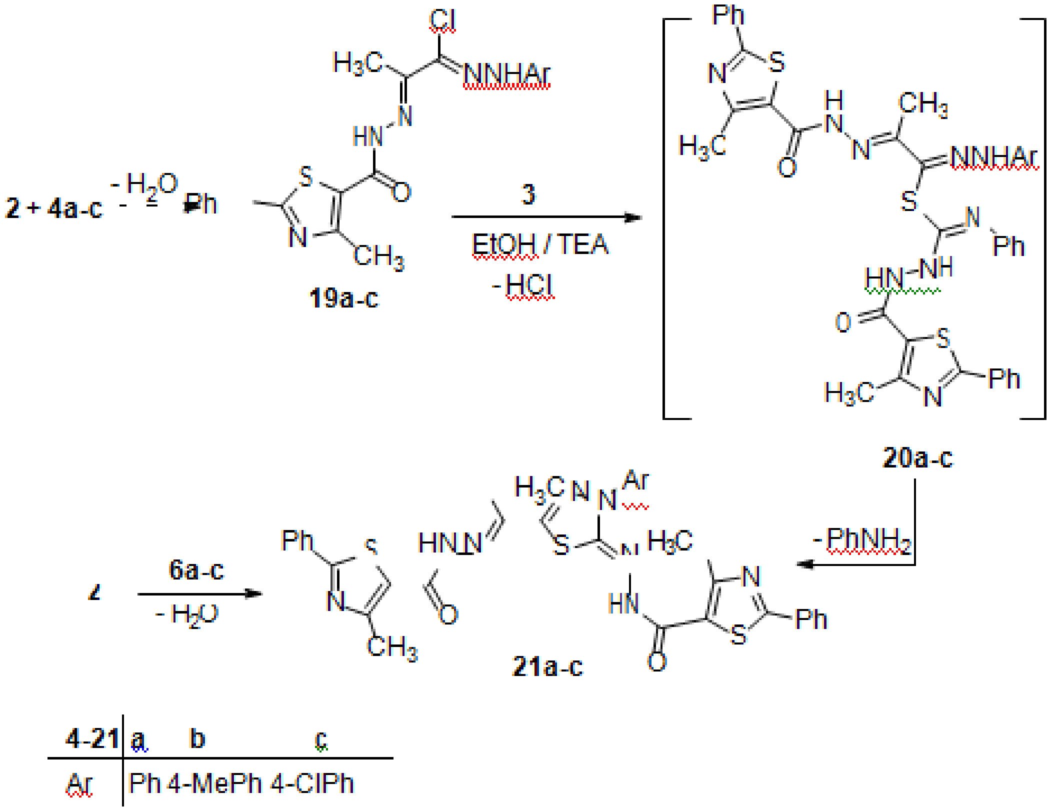
16-18	a	b
Ar	Ph	2,4-(Cl)$_2$Ph

SCHEME 3. Synthesis of thiadiazole derivatives 18a,b

The reaction of 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**) with 2-oxo-*N*-arylpropane hydrazonoyl chlorides **4a–c** in refluxing ethanol gave, in each case, the corresponding condensation product whose elemental analysis and spectra data(see

Experimental) were consistent with structure **19** (Scheme 4). The IR spectra of the latter products exhibited a carbonyl and two NH absorption bands (see experimental part). Their ^{1}HNMR showed two D_2O exchangeable signals of two NH groups in the regions δ 10.03–10.06 and δ 10.57-10.59 ppm. Also, the mass spectra of the latter products confirmed the assigned structure **19** (Scheme 4).

Treatment of thioamide derivative **3** with the appropriate hydrazonoyl halides of type **19a-c** in refluxing EtOH in the presence of TEA gave the corresponding thiadiazole derivatives **21a-c** (Scheme 4). The structures of the isolated products **21a-c** were elucidated on the basis of their spectral data and elemental analysis (see Experimental section). The latter products **21a-c** were alternatively prepared by condensing **6a-c** each with 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**) in refluxing ethanol in quantitative yields (Scheme 4).



4-21	a	b	c
Ar	Ph	4-MePh	4-ClPh

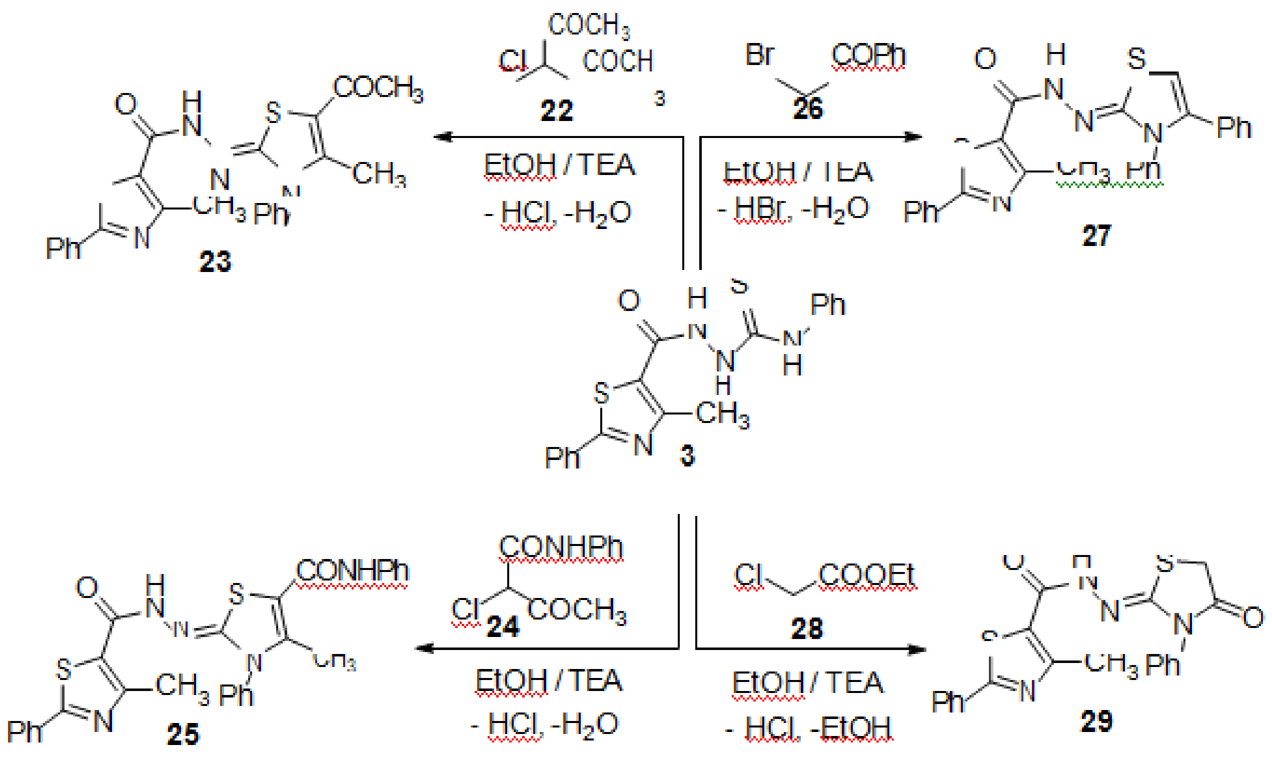
SCHEME 4. Synthesis of thiadiazole derivatives 21a-c

Finally, the starting compound **3** was used for preparation of thiazole derivatives.

Thus, refluxing of compound **3** with 3-chloropentane-2,4-dione (**22**) or 2-chloro-3-oxo-N- phenylbutanamide (**24**) in EtOH in the presence of triethylamine afforded the thiazole derivatives **23** and **25**, respectively, as outlined in Scheme 5.The structure of compounds **23** and **25** were elucidated based on their elemental analysis and spectral data (see Experimental).

Also, thioamide derivative **3** reacted with phenacyl bromide **26** under the same experimental condition to afford one isolable product **27** named as *N*'-(3,4-diphenylthiazol-2(3*H*)-ylidene)- 4-methyl-2-phenylthiazole-5-carbohydrazide (Scheme 5). The structure of the product **27** was established based on its elemental analysis and spectral data (see Experimental).

In a similar manner, thioamide derivative **3** reacted with ethyl chloroacetate (**28**) to afford a single product **29** that was identified as 4-methyl-N'-(4-oxo-3-phenylthiazolidin-2-ylidene)-2- phenylthiazole-5-carbohydrazide (**29**) as outlined in Scheme 3. The structure of the isolated product **29** was established from its elemental analysis and spectral data. Its IR spectrum showed absorption bands at v 3331 (NH), and 1726, 1648 (2C=O) cm^{-1}, its ^{1}H-NMR spectrum showed singlet signal at δ 4.23 ppm due to the thiazolidinone (CH_2) group (see Experimental section).



SCHEME 5.Synthesis of thiazole derivatives 23, 25, 27and 29.

2.2 Cytotoxic activity

The Literature survey showed that many derivatives of thiazole and 1,3,4-thiadiazole have antitumor activity with excellent IG_{50} as depicted in Figure 1 [38-42].

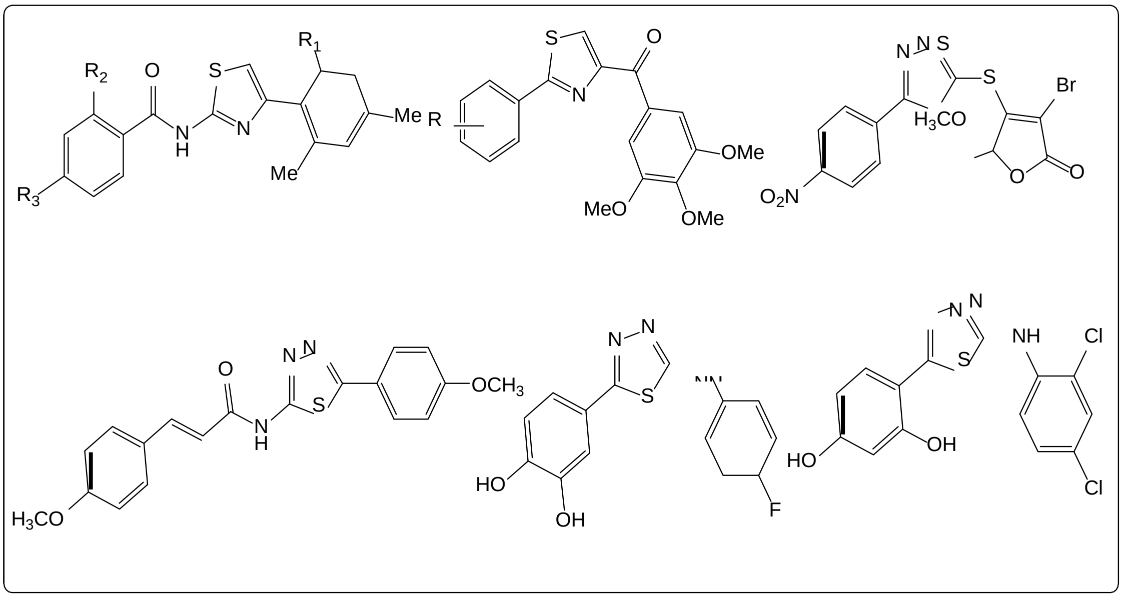


FIGURE 1. Lead compounds among thiazole and thiadiazole derivatives with anticancer activity

In view of these facts, the antitumor activity of the synthesized compounds was determined against a liver carcinoma cell line HepG2. Doxorubicin was used as a reference standard and showed IC_{50} = 0.72 μM against a liver carcinoma cell line. Data generated were used to plot a dose–response curve of which the concentration (μM) of test compounds required to kill 50% of cell population (IC_{50}) was determined. Cytotoxic activity was expressed as the mean IC_{50} of three independent experiments. The results depicted in table **1.**

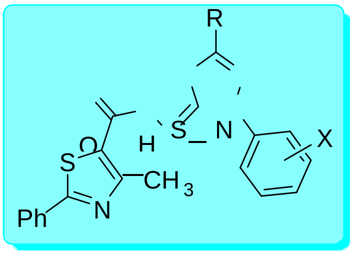
TABLE 1
CYTOTOXIC ACTIVITIES OF TESTED COMPOUNDS AGAINST LIVER CARCINOMA CELL LINE (HEPG2)

Sample Number	R	X	IC$_{50}$ (µM)
Doxorubicin	-----	-----	0.72
6a	Ac	H	9.89
6b	Ac	4-Me	39.06
6c	Ac	4-Cl	1.29
6d	Ac	4-OMe	64.35
6e	Ac	3-Cl	4.03
6f	Ac	4-Br	1.88
6g	Ac	2,4-$(Cl)_2$	1.06
12a	CO_2Et	H	4.70
12b	CO_2Et	4-Me	32.46
12c	CO_2Et	4-Cl	0.91
12d	CO_2Et	2,4-$(Cl)_2$	0.82
18a	CONHPh	H	6.79
18b	CONHPh	2,4-$(Cl)_2$	1.25

The results revealed that most of the tested compounds showed a great variable activity compared to reference drug as shown in Table 1. The order of activity of the newly synthesized compounds was as follow: **6d**< **6b**< **12b**< **6a**< **18a**< **12a**< **6e**< **6f**< **6c**< **18b**< **6g**< **12c**< **12d**

These results lead to the following conclusions.

- The thiadiazole derivatives **12d**,**12c,** **6g**, **18b**, **6c** and **6f** showed high antitumor activity, and the thiadiazole derivatives **6e**, **12a, 18a** and **6a** revealed moderate antitumor activity, while the thiadiazole derivatives **12b, 6b** and **6d** exhibited poor antitumor activity.
- The ester group ($C_{O2}Et$) at position 2 of the thiadiazole ring is necessary to have higher antitumor activity than the acetyl and the N-phenylcarboxamide (CONHPh) groups.
- The presence of chlorine or bromine group (electron-withdrawing groups) at the position 2 or 4 in the aryl moiety of the thiadiazole ring as in the compounds **12d**, **12c,** **6g**, **18b**, **6c** and **6f** increased the cytotoxic activity. Also, halogen at positions 2 or 4 had more cytotoxic activity than halogen at position 3.
- While presence of electron-donating groups such as methyl or methoxy at the position 4 as in the compounds **12b,** **6b** and **6d** decresed the cytotoxic activity.



6a-g, **12a-d**, and **18a,b**

The influence of substituents on the observed biological activity:

a: Type of X = electron withdrawing groups > electron donating groups

FIGURE 2. Structure–activity relationship of tested compounds against liver carcinoma cell line (HepG2)

III. MATERIALS AND METHODS

3.1 Chemistry

3.1.1 General

Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus. IR spectra were measured on PyeUnicam SP 3300 and Shimadzu FTIR 8101 PC infrared spectrophotometers in potassium bromide discs. NMR spectra were meaured on a Varian Mercury VX-300 NMR spectrometer operating at 300 MHz (^{1}H-NMR) and run in deuterated dimethylsulfoxide (DMSO-*d6*). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were measured by using a German made Elementarvario LIII CHNS analyzer. Antitumor activity of the products was measured at the Regional Center for Mycology and Biotechnology at Al-Azhar University, Cairo, Egypt. 2-(4-Methyl-2-phenylthiazole-5-carbonyl)-N-phenylhydrazine carbothioamide (**3**) [35], 5-(4-methyl-2-phenylthiazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione (**9**)[35], hydrazonoyl halides **4a-g, 10a-d** and **16a,b** [36], and ethyl 5-hydrazono-4-phenyl-4,5-dihydro-1,3,4- thiadiazole-2-carboxylate (**15**) [37] were prepared as reported in the respective literature.

3.2 Synthetic Procedures

3.2.1 Synthesis of 1,3,4-thiadiazole derivatives (6a-g, 12a-d and 18a,b).

General procedure. A mixture of compound **3** (0.368 g, 1 mmol) and the appropriate hydrazonoyl chlorides **4a-g** or **10a-d** or **16a,b** (1 mmol) in ethanol (20 mL) containing triethylamine (0.1 g, 1 mmol) was refluxed for 4-6 h. (monitored by TLC). The formed solid product was filtered, washed with methanol, dried and recrystallized from the proper solvents to afford products **6a-g, 10a-d** and **18a,b**, respectively**.** The physical constants and spectral data of the obtained products are listed below:

3.2.1.1 N'-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5- carbohydrazide (6a).

Yellow solid (73%); m.p. 163-165°C (EtOH); IR (KBr) *v* 3317 (NH), 3038, 2951 (CH), 1701, 1647 (2C=O), 1593 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.44 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 6.92-8.00 (m, 10H, ArH), 11.19 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 435 (M^+, 10), 381 (13), 274 (56), 118 (31), 92 (100), 65 (38). Anal. Calcd. for $C_{21}H_{17}N_5O_2S_2$ (435.52): C, 57.91; H, 3.93; N, 16.08. Found C, 57.86; H, 3.84; N, 16.00%.

3.2.1.2 N'-(5-Acetyl-3-(p-tolyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5- carbohydrazide (6b).

Yellow solid (75%); m.p. 149-151°C (EtOH);IR (KBr) *v* 3334 (NH), 3019, 2920 (CH), 1699, 1648 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.31 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 6.98-7.89 (m, 9H, ArH), 11.18 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 449 (M^+, 45), 372 (54), 200 (27), 104 (36), 80 (100), 64 (35). Anal. Calcd. for $C_{22}H_{19}N_5O_2S_2$(449.55): C, 58.78; H, 4.26; N, 15.58. Found C, 58.65; H, 4.17; N, 15.46%.

3.2.1.3 N'-(5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenyl-thiazole-5-carbohydrazide (6c).

Brown solid (75%); m.p. 171-173°C (EtOH); IR (KBr) *v* 3325 (NH), 3013, 2926 (CH), 1698, 1655 (2C=O), 1594 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.45 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 6.93-7.96 (m, 9H, ArH), 11.25 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 471 (M^++2, 14), 469 (M^+, 45), 396 (57), 200 (17), 80(100), 64 (89). Anal. Calcd. for $C_{21}H_{16}ClN_5O_2S_2$ (469.97): C, 53.67; H, 3.43; N, 14.90. Found C, 53.52; H, 3.37; N, 14.82%.

3.2.1.4 N'-(5-Acetyl-3-(4-methoxyphenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenyl-thiazole-5-carbohydrazide(6d).

Brown solid (68%); m.p. 143-145°C (EtOH); IR (KBr) *v* 3328 (NH), 3031, 2923 (CH), 1697, 1653 (2C=O), 1596 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.45 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.99-7.99 (m, 9H, ArH), 11.29 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 465 (M^+, 39), 334 (87), 200 (63), 122 (80), 77 (100), 64 (45). Anal. Calcd. for$C_{22}H_{19}N_5O_3S_2$ (465.55): C, 56.76; H, 4.11; N, 15.04. Found C, 56.63; H, 4.04; N, 14.95%.

3.2.1.5 N'-(5-Acetyl-3-(3-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5 carbohydrazide(6e).

Yellow solid (70%); m.p. 166-168°C (EtOH); IR (KBr) *v* 3431(NH), 3025, 2932 (CH), 1698, 1659 (2C=O), 1593 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.44 (s, 3H, CH_3), 2.66 (s,3H, CH_3), 6.98-7.90 (m, 9H, ArH), 11.23 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 471 (M^++2, 10), 469 (M^+, 34), 334 (46), 200 (28), 132 (48), 80 (100), 64 (68). Anal. Calcd. for $C_{21}H_{16}ClN_5O_2S_2$ (469.97): C, 53.67; H, 3.43; N, 14.90. Found C, 53.60; H, 3.36; N, 14.79%.

3.2.1.6 N'-(5-Acetyl-3-(4-bromophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenyl thiazole-5-carbohydrazide (6f).

Brown solid (73%); m.p. 160-162°C (EtOH); IR (KBr) *v* 3429 (NH), 3012, 2924 (CH), 1696, 1654 (2C=O), 1594 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.44 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 6.95-7.94 (m, 9H, ArH), 11.25 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 516 (M^++2, 51), 514 (M^+, 53), 325 (76), 172 (44),91 (80), 80 (100), 64 (47). Anal. Calcd. for $C_{21}H_{16}BrN_5O_2S_2$ (514.42): C, 49.03; H, 3.14; N, 13.61. Found C, 48.93; H, 3.12; N, 13.53%.

3.2.1.7 N'-(5-Acetyl-3-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenyl thiazole-5-carbohydrazide(6g).

Brown solid (77%); m.p. 181-183°C (EtOH/dioxane); IR (KBr) *v* 3318 (NH), 3088, 2926 (CH), 1699, 1671 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.47 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 6.97-8.07 (m, 8H, ArH), 11.19 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 504 (M^+, 14), 407 (33), 161 (14), 80 (99), 64 (100). Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O_2S_2$ (504.41): C, 50.00; H, 3.00; N, 13.88. Found C, 49.88; H, 2.92; N, 13.75%.

3.2.1.8 Ethyl 5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4-phenyl-4,5-dihydro-1,3,4- thiadiazole-2-carboxylate (12a).

Yellow solid (71%); m.p. 137-139 °C (EtOH); IR (KBr) *v* 3432 (NH), 3035, 2923 (CH), 1749, 1659 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 1.20 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H_3}$), 2.74 (s, 3H, CH_3), 4.21 (q, 2H, *J* = 7.1 Hz, $C\underline{H_2}CH_3$),7.00-8.01 (m, 10H, ArH), 10.72 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%): 465 (M^+, 27), 334 (50), 200 (34), 104 (40), 80 (100), 64 (37). Anal. Calcd. for$C_{22}H_{19}N_5O_3S_2$ (465.55): C, 56.76; H, 4.11; N, 15.04. Found C, 56.69; H, 4.03; N, 15.01%.

3.2.1.9 Ethyl 5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4- thiadiazole-2-carboxylate (12b).

Yellow solid (70%); m.p. 147-149°C (EtOH); IR (KBr) *v* 3424 (NH), 3058, 2925 (CH), 1749, 1674 (2C=O), 1595 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 1.20 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H_3}$), 2.26 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.19 (q, 2H, *J* = 7.1 Hz, $C\underline{H_2}CH_3$),7.00-8.02 (m, 9H, ArH), 10.73 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 479 (M^+, 20), 367 (25), 251 (18), 80 (85), 64 (100). Anal. Calcd. for $C_{23}H_{21}N_5O_3S_2$ (479.57): C, 57.60; H, 4.41; N, 14.60. Found C, 57.49; H, 4.33; N, 14.51%.

3.2.1.10 Ethyl 4-(4-chlorophenyl)-5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4,5- dihydro-1,3,4-thiadiazole-2-carboxylate(12c).

Yellow solid (73%); m.p. 167-169°C (EtOH/dioxane); IR (KBr) *v* 3340 (NH), 3050, 2927 (CH), 1748, 1670 (2C=O), 1599 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 1.23 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H_3}$), 2.75 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.1 Hz, $C\underline{H_2}CH_3$),7.02-7.96 (m, 9H, ArH), 10.77 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 501 (M^++2, 13), 499 (M^+, 45), 363 (39), 334 (100), 200 (35), 104 (30), 77 (50). Anal. Calcd. for $C_{22}H_{18}ClN_5O_3S_2$ (499.99): C, 52.85; H, 3.63; N, 14.01. Found C, 52.79; H, 3.60; N, 13.87%.

3.2.1.11 Ethyl 4-(2,4-dichlorophenyl)-5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4,5- dihydro-1,3,4-thiadiazole-2-carboxylate (12d).

Brown solid (75%); m.p. 173-175°C (EtOH/dioxane); IR (KBr) *v* 3221 (NH), 3079, 2926 (CH), 1749, 1671 (2C=O), 1599 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 1.24 (t, 3H, *J* = 7.1 Hz, $CH_2C\underline{H_3}$), 2.77 (s, 3H, CH_3), 4.23 (q, 2H, *J* = 7.1 Hz, $C\underline{H_2}CH_3$),7.08-8.13 (m, 8H, ArH), 10.77 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 534 (M^+, 19), 449 (78), 223(100), 200 (54), 104 (58), 80 (85). Anal. Calcd. for $C_{22}H_{17}Cl_2N_5O_3S_2$(534.44): C, 49.44; H, 3.21; N, 13.10. Found C, 49.29; H, 3.16; N, 13.02%.

3.2.1.12 5-(2-(4-Methyl-2-phenylthiazole-5-carbonyl)hydrazono)-N,4-diphenyl-4,5-dihydro-1,3,4- thiadiazole-2-carboxamide (18a).

Brown solid (76%); m.p. 176-178°C (EtOH/dioxane); IR (KBr) *v* 3427, 3343 (2NH), 1672, 1653 (2C=O), 1597 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) *δ* 2.75 (s, 3H, CH_3), 7.02-7.78 (m, 15H, ArH), 10.18(s, br, 1H, D_2O-exchangeable NH), 11.72 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 512 (M^+, 8), 401 (00), 282 (10), 150 (22), 92 (26), 65 (29). Anal. Calcd. For $C_{26}H_{20}N_6O_2S_2$ (512.61): C, 60.92; H, 3.93; N, 16.39. Found C, 60.78; H, 3.85; N, 16.32%.

3.2.1.13 4-(2,4-Dichlorophenyl)-5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-N- phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (18b).

Brown solid (77%); m.p. 186-188°C (Dioxane); IR (KBr) *v* 3429, 3337(2NH), 1692, 1656 (2C=O), 1591 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) *δ* 2.76 (s, 3H, CH_3), 7.13-7.83 (m, 13H, ArH), 10.19(s, br, 1H, D_2O-exchangeable NH), 11.77 (s, br, 1H D_2O-exchangeable NH); MS *m/z* (%) 581 (M^+, 38), 473 (64), 334 (72), 200 (35), 119 (65), 64 (100). Anal. Calcd. for $C_{26}H_{18}Cl_2N_6O_2S_2$ (581.50): C, 53.70; H, 3.12; N, 14.45. Found C, 53.62; H, 3.03; N, 14.32%.

3.2.2 Alternate synthesis of thiadiazole derivatives 6a and 18a

To a mixture of 5-(4-methyl-2-phenylthiazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione (**9**) (0.275 g, 1 mmol) and hydrazonoyl chloride **4a** or **16a** (1 mmol) in absolute EtOH (25 mL), was added triethylamine (0.1g, 0.14 mL, 1 mmol). The reaction mixture was stirred at room temperature till methyl mercaptan ceased to evolve (3h). The solvent was evaporated and the residue was treated with ice/HCl mixture. The solid product was collected by filteration, washed with EtOH, dried, and recrystallized to give the respective compounds **6a**, and **18a**, that was identical in all respects (m.p., mixed m.p. and IR spectra) with that obtained from reaction of **4a** or **16a** with **3.**

3.2.3 Aternate synthesis of 12a

A mixture of ethyl 4-methyl-2-phenylthiazole-5-carboxylate (**1**)(0.247 g, 1 mmol) and ethyl 5-hydrazono-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**15**) (0.264g, 1 mmol) was refluxed in ethanol for 4 h. The solid product that separated was filtered off, washed with water and finally recrystallized to give the corresponding product, **12a** which was identical in all aspects (m.p., mixed m.p. and IR spectra) with those obtained from reaction of **3** with **10a.**

3.2.4 Synthesis of hydrazonoyl chlorides 19a-c

A mixture of 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**) (2.33 g, 10 mmol) and the appropriate hydrazonoyl chlorides **4a-c** (10mmol) in ethanol (30 mL) was refluxed for 3 hr. The resulting solid product was collected and recrystallized from the proper solvent to give the corresponding products**19a-c**.

3.2.4.1 2-(2-(4-Methyl-2-phenylthiazole-5-carbonyl)hydrazono)-N'-phenylpropanehydrazonoyl chloride (19a).

Yellow solid (84%); m.p. 188-190°C (EtOH); IR (KBr) *v* 3440, 3316(2NH), 3036, 2922(CH), 1640 (C=O), 1599 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) *δ* 2.36 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.06-7.86 (m, 10H, ArH), 10.03 (s, br, 1H, D_2O-exchangeable NH), 10.57 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%): 413 (M^++2, 12), 411 (M^+, 40), 375 (48), 202 (100), 174 (45), 71 (26). Anal. calcd for $C_{20}H_{18}ClN_5OS$ (411.91): C, 58.32; H, 4.40; N, 17.00.Found: C, 58.19; H, 4.37; N, 16.88%.

3.2.4.2 2-(2-(4-Methyl-2-phenylthiazole-5-carbonyl)hydrazono)-N'-(p-tolyl)propane- hydrazonoylchloride (19b).

Yellow solid (86%); m.p. 172-174 °C (EtOH);IR (KBr) *v* 3437, 3313 (2NH), 3041, 2917 (CH), 1679(C=O), 1598 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d6*) *δ* 2.24 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.08-7.99 (m, 9H, ArH), 10.06(s, br, 1H, D_2O-exchangeable NH), 10.59 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 427 (M^++2, 10), 425 (M^+, 33), 389 (26), 202 (81), 106 (100), 64 (66). Anal. calcd for $C_{21}H_{20}ClN_5OS$ (425.93): C, 59.22; H, 4.73; N, 16.44. Found: C, 59.18; H, 4.65; N, 16.37%.

3.2.4.3 N'-(4-Chlorophenyl)-2-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)propane- hydrazonoyl chloride (19c).

Yellow solid (87%); m.p. 194-196°C (DMF); IR (KBr) *v* 3434, 3319 (2NH), 3044, 2926(CH), 1682 (C=O), 1593 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.37 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 7.08-7.99 (m, 9H, Ar-H), 10.06 (s, br, 1H, D_2O-exchangeable NH), 10.57(s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 446 (M^+, 8), 283 (14), 202 (39), 104 (46), 80 (100), 64 (90). Anal. calcd for $C_{20}H_{17}Cl_2N_5OS$ (446.35): C, 53.82; H, 3.84; N, 15.69. Found: C, 53.75; H, 3.79; N, 15.58%.

3.2.5 Synthesis of 1,3,4-thiadiazole derivatives 21a-c.

Method A: A mixture of compound **3** (0.368 g, 1 mmol) and the appropriate hydrazonoyl chlorides **19a-c** (1 mmol) in ethanol (20 mL) containing triethylamine (0.1 g, 1 mmol) was refluxed for 6 h.. The formed solid produt was filtered,, washed with methanol, dried and recrystallized from the suitable solvents to give corresponding products **21a–c.**

3.2.5.1 4-Methyl-N'-(1-(-5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)-2-phenylthiazole-5-carbohydrazide (21a).

Yellow solid(74%); m.p. 162-164°C (EtOH); IR (KBr) *v* 3421, 3307 (2NH), 3031, 2951 (CH), 1649 (C=O), 1596 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.34 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 2.76(s, 3H, CH_3), 6.97-8.14 (m, 15H, ArH), 10.18 (s, br, 1H, D_2O-exchangeable NH), 11.17 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 650 (M^+, 34), 526 (30), 416 (60), 358 (28), 104 (55), 64 (100). Anal. Calcd for $C_{32}H_{26}N_8O_2S_3$ (650.80): C,59.06; H, 4.03; N, 17.22. Found C, 58.94; H, 4.01; N, 17.07%.

3.2.5.2 4-Methyl-N'-(1-(5-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethylidene)-2-phenylthiazole-5-carbohydrazide(21b).

Yellow solid (72%); m.p. 149-151°C (EtOH); IR (KBr) *v* 3422, 3328 (2NH), 3053, 2929 (CH), 1647 (C=O), 1597 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.26 (s, 3H, CH_3),2.35 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.76(s, 3H, CH_3), 6.91-8.03 (m, 14H, ArH), 10.18 (s, br, 1H, D_2O-exchangeable NH), 11.14 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 664 (M^+, 35), 553 (60), 334 (19), 202 (65), 104 (85), 64 (100). Anal. Calcd for $C_{33}H_{28}N_8O_2S_3$ (664.82): C, 59.62; H, 4.25; N, 16.85. Found C, 59.47; H, 4.17; N, 16.79%.

3.2.5.3 N'-(3-(4-Chlorophenyl)-5-(1-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-ethyl)- 1,3,4-thiadiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide (21c).

Yellow solid (76%); m.p. 191-193°C (Dioxane); IR (KBr) *v* 3424, 3312 (2NH), 3047, 2932 (CH), 1649 (C=O), 1599 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.33 (s, 3H, CH_3), 2.66 (s, 3H, CH_3), 2.77(s, 3H, CH_3), 6.90-8.11 (m, 14H, ArH), 10.13 (s, br, 1H, D_2O-exchangeable NH), 11.19 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 686 (M^++2, 8), 684 (M^+, 26), 513 (53), 368 (39), 257 (17), 104 (25), 64 (100). Anal. Calcd for $C_{32}H_{25}ClN_8O_2S_3$ (685.24): C, 56.09; H, 3.68; N, 16.35. Found C, 56.02; H, 3.58; N, 16.22%.

Method B: A mixture of 4-methyl-2-phenylthiazole-5-carbohydrazide (**2**) (0.233 g, 1 mmol) and the appropriate 1,3,4-thiadiazoles **6a-c** (1 mmol) in ethanol (10 mL) was refluxed for 4h, allowed to cool and the solid product that formed was filtered off, washed with EtOH, dried and recrystallized from the proper solvent to give the corresponding product, **21a-c** which were identical in all aspects (m.p., mixed m.p. and IR spectra) with those obtained from reaction of **3** with **19a-c.**

3.2.6 General procedure for the synthesis of thiazole derivatives 23, 25, 27, and 29

A mixture of compound **3**(0.368 g, 1 mmol) and the appropriate α-halo-compounds namely, 3-chloropentane-2,4-dione (**22**), 2-chloro-3-oxo-N-phenylbutanamide (**24**), 2-bromo-1-phenyl ethanone (**26**) and ethyl 2-chloroacetate (**28**) (1 mmol for each) in ethanol (20 mL) containing triethylamine (0.1 g, 1 mmol) was refluxed for 4-6 h. (monitored by TLC The solid product was filtered, washed with water, dried and recrystallized from the proper solvent to give the corresponding thiazole derivatives **23**, **25**, **27**and **29**, respectively.

3.2.7 N'-(5-Acetyl-4-methyl-3-phenylthiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5- carbohydrazide (23).

Yellow solid (78%); m.p. 155-157°C (EtOH); IR (KBr) *v* 3432 (NH), 3036, 2993 (CH), 1695, 1648 (2C=O), 1590 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) δ 2.32 (s, 3H, CH_3),2.46 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 6.91-7.86 (m, 10H, ArH), 10.61 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 448 (M^+, 57), 246 (60), 176 (35), 104 (80), 77 (100). Anal. Calcd for $C_{23}H_{20}N_4O_2S_2$ (448.56): C, 61.59; H, 4.49; N, 12.49. Found C, 61.48; H, 4.36; N, 12.37%.

3.2.7.1 Methyl-2-(2-(4-methyl-2-phenylthiazole-5-carbonyl)hydrazono)-N-3-diphenyl-2,3-dihydr othiazole-5-carboxamide (25).

Yellow solid (79%); m.p. 182-84°C (DMF); IR (KBr): *ν* 3435, 3176(2NH), 3030, 2928(CH), 1671, 1649 (2C=O), 1594 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.36 (s, 3H, CH_3),2.76(s, 3H, CH_3), 6.97-7.73 (m, 15H, ArH), 10.46 (s, br, 1H, D_2O-exchangeable NH), 11.72 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 525 (M^+, 7), 447 (16), 334 (100), 200 (59), 77 (89). Anal. Calcd for $C_{28}H_{23}N_5O_2S_2$ (525.64): C, 63.98; H, 4.41; N, 13.32. Found C, 63.84; H, 4.30; N, 13.28%.

3.2.7.2 N'-(3,4-Diphenylthiazol-2(3H)-ylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide(27).

Yellow solid (70%); m.p. 174-178°C (EtOH); IR (KBr) *ν* 3369(NH), 3047, 2926(CH), 1648 (C=O), 1594 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.75 (s, 3H, CH_3), 7.03 (s, 1H, thiazole-H_5), 7.35-8.02 (m, 15H, ArH), 10.73 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 468 (M^+, 25), 334 (100), 200 (40), 104 (69), 64(65). Anal.Calcd for $C_{26}H_{20}N_4OS_2$ (468.59): C, 66.64; H, 4.30; N, 11.96. Found C, 66.55; H, 4.21; N, 11.79%.

3.2.7.3 4-Methyl-N'-(4-oxo-3-phenylthiazolidin-2-ylidene)-2-phenylthiazole-5-carbohydrazide (29).

Yellowish-white solid (72%); m.p. 192-194°C (Dioxane); IR (KBr) *ν* 3331(NH), 3036, 2926 (CH), 1726, 1648 (2C=O), 1596 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-*d*6) *δ* 2.65 (s, 3H, CH_3), 4.23 (s, 2H, thiazolone-CH_2), 7.40-7.88 (m, 10H, ArH), 10.82 (s, br, 1H, D_2O-exchangeable NH); MS *m/z* (%) 408 (M^+, 65), 334 (18), 202 (100), 104 (86), 64 (69). Anal. Calcd for $C_{20}H_{16}N_4O_2S_2$ (408.50): C, 58.80; H, 3.95; N, 13.72. Found C, 58.68; H, 3.84; N, 13.64%.

3.3 Evaluation of the antitumor activity using Viability assay:

Human hepatocellular carcinoma (HepG2) cell line was obtained from the American Type Culture Collection (ATCC, Rockville, MD). The cells were grown on RPMI-1640 medium supplemented with 10% inactivated fetal calf serum and 50 µg/mL gentamycin. The cells were maintained at 37 ^{O}C in a humidified atmosphere with 5% carbon dioxide and were subcultured 2 to 3 times a week. Potential cytotoxicity of the tested compounds was evaluated on tumor cells using the reported method of Gangadevi and Muthumary [43]. The cells were grown as monolayers in growth RPMI-1640. The monolayers of 10^4 cells adhered at the bottom of the wells in a 96-well microtiter plate incubated for 24 h at 37 ^{O}C in a humidified incubator with 5% carbon dioxide. The monolayers were then washed with sterile phosphate buffered saline (0.01 M pH 7.2) and simultaneously the cells were treated with 100 µL from different dilutions of tested sample in fresh maintenance medium and incubated at 37 ^{O}C. A control of untreated cells was made in the absence of tested sample. Positive controls containing doxroubcin drug was also tested as reference drug for comparison. Six wells were used for each concentration of the test sample. Every 24 h the observation under the inverted microscope was made.The number of the surviving cells was determined by staining the cells with crystal violet [44] followed by cell lysing using 33% glacial acetic acid and read the absorbance at 590 nm using microplate reader (SunRise, TECAN, Inc, USA) after well mixing. The absorbance values from untreated cells were considered as 100% proliferation. The number of viable cells was determined using microplate reader as previously mentioned before and the percentage of viability was calculated as [1-(ODt/ODc)] x 100% where ODt is the mean optical density of wells treated with the tested sample and ODc is the mean optical density of untreated cells. The relation between surviving cells and drug concentration is plotted to get the survival curve of each tumor cell line after treatment with the specified compound. The 50% inhibitory concentration (IC_{50}), the concentration required to cause toxic effects in 50% of intact cells, was estimated from graphic plots.

IV. CONCLUSIONS

In this context, a series of novel thiazoles and 1,3,4-thiadiazoles bearing thiazole were synthesized. The structure of the newly prepared compounds was established based on both elemental analysis and spectroscopic data and by an alternative method wherever possible. Moreover, the mechanisms of formation of the title compounds were discussed. Some of the synthesized compounds were evaluated for their anti-cancer activity against the human hepatocellular carcinoma (HepG2) cell line. The results showed that the thiadiazole derivatives **12d**, **12c, 6g**,**18b**, **6c** and **6f** having IC_{50} values 0.82, 0.91, 1.06, 1.25, 1.29 and 1.88 µM, respectively, were found to be the highly active compounds of the prepared series. Based on the experimental results of the antitumor activity, the structure-activity relationships were discussed.

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AUTHOR CONTRIBUTIONS

S.M.G. designed research; S.M.G., M.R.A. and N.A.K. performed research and analyzed the data; S.M.G., N.A.K. and Y.N.M. wrote and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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