chemistry proceedings

MDPI

Research paper

An Efficient Synthesis of Novel Hydrazine-Carboxamides In Water-Ethanol Solvent System as anticancer agents.

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Abstract: Hydrazine-carboxamide has shown a promising anticancer activity. A series of novel Hydrazine-carboxamide derivatives were synthesised and were identified by TCL method using suitable solvent system, also they are confirmed by determination of there melting point. Novel series of Hydrazine-carboxamides is synthesised using water-ethanol (2:1) solvent system. The method reported is efficient as it is less time consuming with good yields. Overall insilico study was performed for the ligands by molecular docking against EGFR. The EGFR (PDB: 3W2R) structure with high resolution was obtained from the protein data bank. The ligands were saved as mol file and the docking was done as per the protocol. Some Ligands shown good binding with EGFR protein sites, ligand 4c shown docking score of -7.138 & can be further explore and evaluate for significant anticancer activity.

Keywords: Hydrazine-carboxamide; Anticancer activity; water-ethanol solvent system.

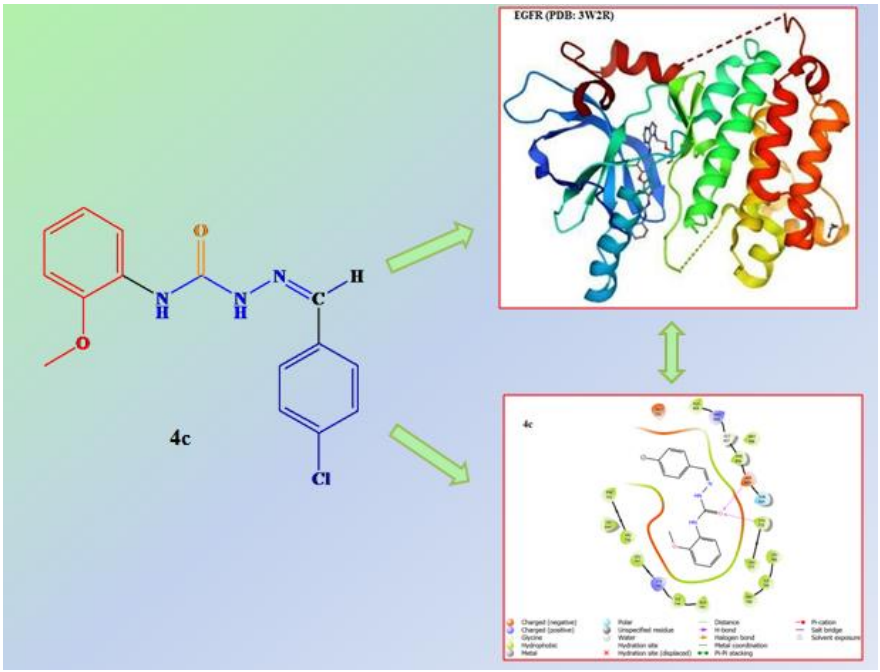

Figure 1: Graphical Abstract:

Citation: Agarwal, M.; Sharma, V.; Sharma, P.; Ahsan ,J.; Title. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Published: date

1. Introduction

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer[1].The most common causes of cancer death are cancers of Lung, Colorectal, Stomach, Liver and Breast.[2]

According to World Health organization (WHO), Total number of new cases in India were 1,157,294 (among males was 570,045 and among female was 587,249) for the year 2018, The most common cancers in 2018 were Breast (14%), Lip and oral cavity (10.4%), Cervix uteri (8.4%), Lung (5.9%), Stomach (5%).[3]

According to the latest report from, National Cancer Registry Programme (NCRP), India. The projected number of total patients with cancer in India is 1,392,179 [among males was 679,421 (94.1 per 100,000) and among females 712,758 (103.6 per 100,000)] for the year 2020.[4]

Treatment of cancer with the available anticancer drugs is associated with various adverse effects viz. bone marrow depression, alopecia, drug induced cancer, etc. Chemotherapy with anticancer drugs is often associated with cytotoxicity, genotoxicity to normal cells and resistance development.

Investigation of the biology and chemistry of novel anticancer agent is need of the time. Medicinal chemists are showing great perseverance in search of newer and safer anticancer agents.

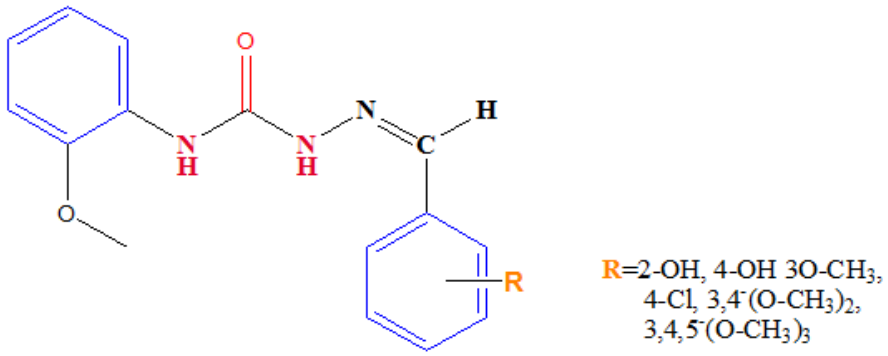

Figure 2: Design of newer Hydrazine-Carboxamides scaffolds as biologically active agents (4a-e) [5]

2. Materials and Methods:

The hydrazine carboxamide [8] analogues (4a-e) described in this study are shown in Table 1 and the reaction sequence for their synthesis is shown in Scheme 1.

A series of novel Substituted hydrazine-carboxamide analogues were synthesized involving three step process. In the initial step substituted aromatic amines (o-Anisidine 0.1mol, 11.2 gm) (1) was treated with sodium cyanate (0.1 mol, 6.5 gm) equimolar in the presence of glacial acetic acid (GAA) 20ml in 80ml of hot water with continuous stirring to form substituted phenyl urea (2) in the subsequent step which will then be refluxed for 48 h with hydrazine hydrate (equimolar) using alcohol as solvent system to obtain substituted 2-methoxy phenyl semicarbazide.[9] In the final step 2-methoxy phenyl semicarbazide and substituted aromatic aldehydes were condensed using water-ethanol (2:1) solvent system to obtain final novel series of 2-(substituted benzylidene/ethylidene)-N-(substituted phenyl) hydrazine carboxamide (4a-e).

The method reported is efficient as it is less time consuming with good yields. The hydrazine carboxamide analogues were synthesized as per the reported method. The yields of the title compounds were ranging from 80% to 90% after recrystallization with absolute ethanol. The completion of reaction was monitored by thin layer chromatography (TLC) using mobile phase chloroform–methanol (9:1).

2.1 Molecular docking studies:

The molecular docking against EGFR was performed for the ligands **(4a-e)**. The EGFR (PDB: 3W2R) [6] [7] structure with high resolution was obtained from the protein data bank. The ligands were saved as mol file and the docking was done as per the protocol. Some Ligands shown good binding with EGFR protein sites, ligand **4c** shown docking score of **-7.138.**

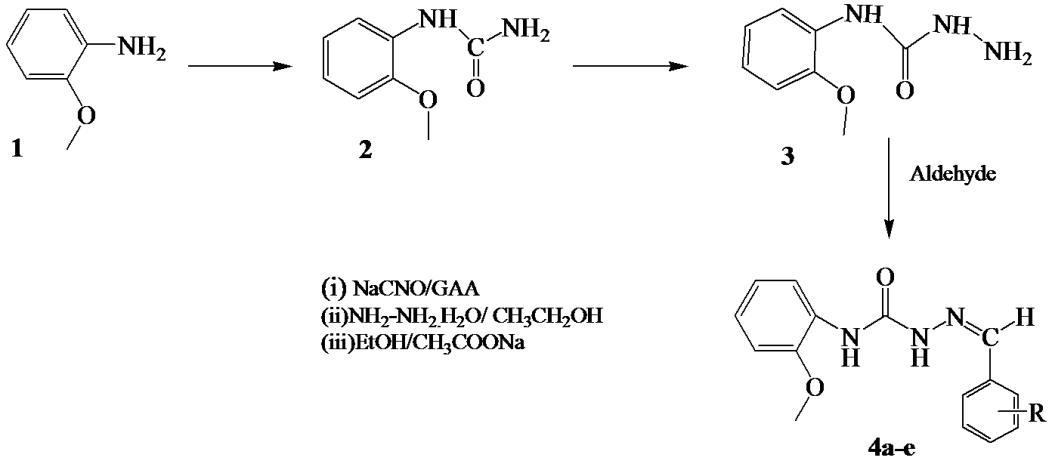

Figure 3: Scheme 1. Protocol for the synthesis of *2-(substituted benzylidene/ethylidene)-N-(substituted phenyl) hydrazine carboxamide analogues* (4a-e).

Compounds	R	Yield(%)	M.P. (∘ C)	Rf Value
4a	2-Hydoxy	85	180-182	0.65
4b	4-Hydroxy-3-Methoxy	87	204-206	0.72
4c	4-Chloro	89	244-246	0.62
4d	3,4-Dimethoxy	86	166-168	0.58
4e	3,4,5-Trimethoxy	84	218-220	0.49

Table 1. Physical constants of 2-(substituted benzylidene/ethylidene)-N-(substituted phenyl) hydrazine carboxamide (4a-e).

3. Results and discussion

3.1 Molecular docking studies:

The molecular docking against EGFR was performed for the ligands (4a-e). The EGFR (PDB: 3W2R) The ligands were saved as mol file and the docking was done as per the protocol. Novel molecule 4c show highest docking score -7.138, ligand shown efficient H-bonding with amino acid (ASP855 & CYS775) with EGFR (PDB: 3W2R). Remaining ligands 4a, 4b, 4d, 4e also reported appreciable docking score of -6.715, -6.507, -5.914, -6.746 respectively.[10]

The molecular docking studies against EGFR was done as per the reported protocol. The various types of interactions including H-bond, p-p stacking and halogen bond were observed in the molecular docking studies and the results of docking studies are summarized in Table 2. The compounds 4a, 4b, 4c, 4d and 4e showed two H-bonds interaction within the active site of EGFR.[11]

A H-bond between the phenolic function and the residue Gly857 & Phe856 and another H-bond between the carbonyl function and the residue Asp855 & Cys775 was observed in ligand 4a. A H-bond between the phenolic function and the residue Asn842 and another H-bond between the carbonyl function and the residue Thr854 through H2O

molecule was observed in ligand 4b. H-bond between the carbonyl function and the residue Asp855 & Cys775 was observed in ligand 4c. H-bond between the carbonyl function and the residue Thr854 through H2O molecule was observed in ligand 4d. H-bond between the carbonyl function and the residue Thr854 through H2O molecule was observed in ligand 4e.

S. No.	Ligand	Docking Score	Types of interaction
1	4a	-6.715	H-bond with (Gly857) (Phe856) (Asp855) & (Cys775)
2	4b	-6.507	H-bond with (Asn842) & (Thr854)
3	4c	-7.138	H-bond with (Asp855) & (Cys775)
4	4d	-5.914	H-bond with (Thr854)
5	4e	-6.746	H-bond with (Thr854)

Table 2: The molecular docking studies of ligands 4a-e against the active site EGFR.

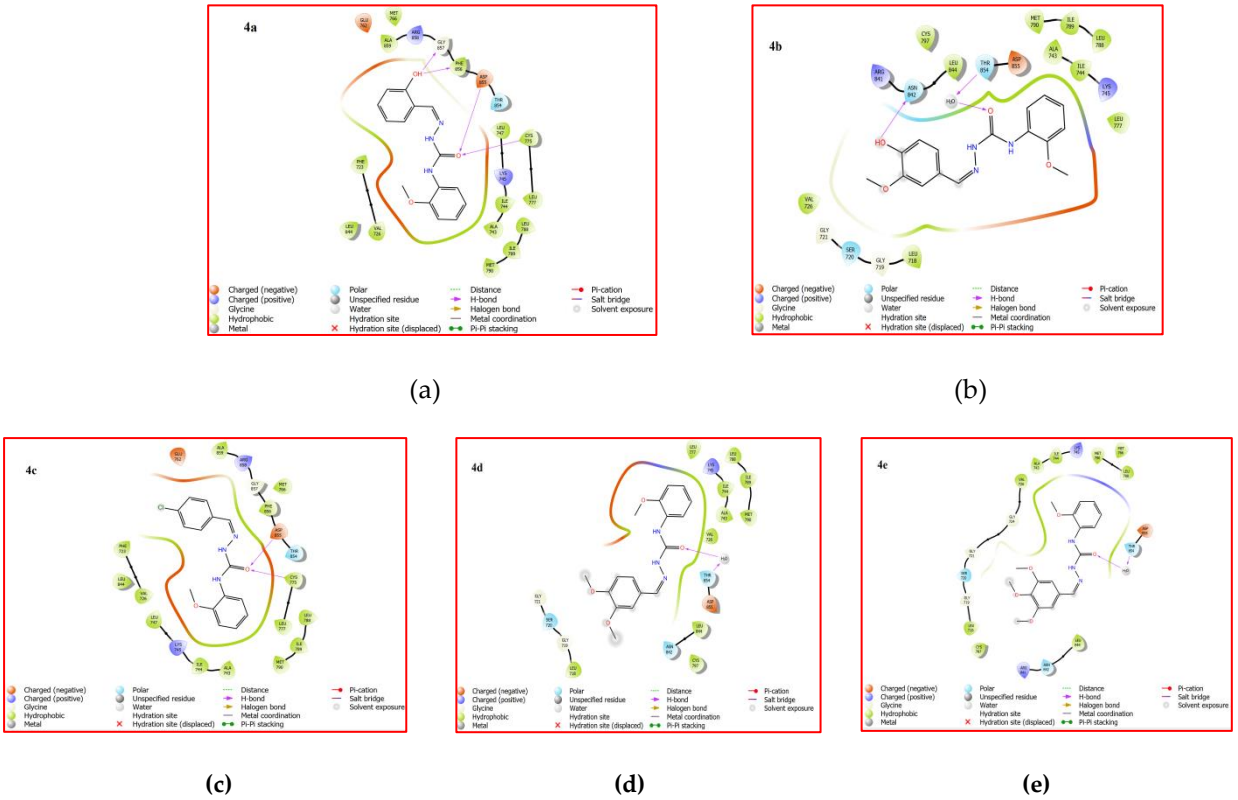

Figure 4. (**a**) The images of 2D interactions of compounds 4a: H-bond with (Gly857) (Phe856) (Asp855) & (Cys775) **(b)** 2D interactions of compounds 4b: H-bond with (Asn842) & (Thr854) **(c**) 2D interactions of compounds 4c: H-bond with (Asp855) & (Cys775) **(d)** 2D interactions of compounds 4d: H-bond with (Thr854) **(e)** 2D interactions of compounds 4e: H-bond with (Thr854)

4. Conclusions

All the synthesized compounds were obtained in satisfactory yields and evaluated for their insilico study by molecular docking. The compound 4c, which expressed maximum binding with (EGFR PDB: 3W2R) with highest docking score of -7.138 is expected to possess good anticancer activity & could be considered as lead for further exploration and evaluation for anticancer activity & drug discovery. Synthesis of other series of hydra-

zine-carboxamide analogues is in progress in our laboratory. The hydrazine-carboxamide derivatives discovered in this study may provide valuable information in the field of drug design and discovery.

Acknowledgments:
I consider myself most lucky to work under the guidance of Dr. Vandana Sharma; Dr. Md. Jawed Ahsan; I take this opportunity to express my heartfelt gratitude to my reverend guide. I am very much grateful to him for his invaluable guidance and everlasting encouragement throughout my course.
The people holding the management of Arya College of pharmacy, Jaipur, Rajasthan & Maharishi Arvind college of Pharmacy, Jaipur, Rajasthan, India is acknowledged for providing research facilities
I am immensely thankful to Dr. Piush Sharma, Principal, Maharishi Arvind college of Pharmacy, Ambabari, Jaipur for providing me the necessary facilities and help in carrying out my research work.

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