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Acrylamide Moiety, a Valuable Fragment in Medicinal Chemistry: Insight into Synthetic Methodologies, Chemical Reactivity and Spectrum of Biological Activities of Acrylamide Derivatives

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ABSTRACT

Acrylamide moiety is a pronounced Michael acceptor that has drawn much interest in a wide array of drugs designed for various therapeutic purposes. Herein we outline different synthetic pathways, scientific bases for its chemical reactivity and how it is functionalized for design of new therapeutic entities, in addition to a brief insight into spectrum of reported biological activities of acrylamide containing compounds up to date.

Keywords: *Acrylamide; Antitumor; Covalent inhibitors; Kinase inhibitors, Michael acceptor*

INTRODUCTION

Acrylamide moiety has been proved to be a valuable tool for design of novel therapeutic entities. Evidence for that is observed through the wide range of biological activities exhibited by acrylamide derivatives including antitumor activity[1], epidermal growth factor receptor (EGFR) kinase inhibitor activity[2], antiviral activity[3], anti-inflammatory activity[4], antiplatelet activity[5], antidiabetic activity[6], tubulin polymerization inhibitor activity[7], antibacterial activity[8], vasodilator activity[9], antifungal activity[10], angiotensin II receptor antagonist activity[11] and histone deacetylase HDAC inhibitor activity[12]. A considerable number of approved drugs incorporate acrylamide moiety in their structures, for example: **Entacapone** a catechol *O*-methyl transferase (COMT) inhibitor used for treatment of Parkinson disease. In addition, **Panobinostat** a HDAC inhibitor approved in February 2015 for the treatment of multiple myeloma. In the same context **Belinostat** HDAC inhibitor approved in July 2014 for treatment of peripheral *T*-cell lymphoma. Additionally, **Ibrutinib**, a Bruton's tyrosine kinase BTK inhibitor approved 2013 for treatment of various myeloid tumors. **Rifampicin**, a well-known antibiotic approved for treatment of mycobacterial infections as tuberculosis and leprosy. **Anthramycin** an antibiotic and antineoplastic drug. **Afatinib** EGFR kinase approved for treatment of non-small cell lung cancer (NSCLC), **Carnetinib** and **Dacomitinib** EGFR kinase inhibitors phase II clinical trials drugs for treatment of NSCLC **Figure 1**.

1. Synthetic pathways

1.1. Knovenagel condensation

Knovenagel originally reported the condensation of aldehydes with diethyl malonate in basic medium to yield alkylidene malonic acid diesters[13], **Scheme 1**. Dobner reported the modification of Knovenagel condensation by carrying out the reaction between aldehydes and malonic acid in

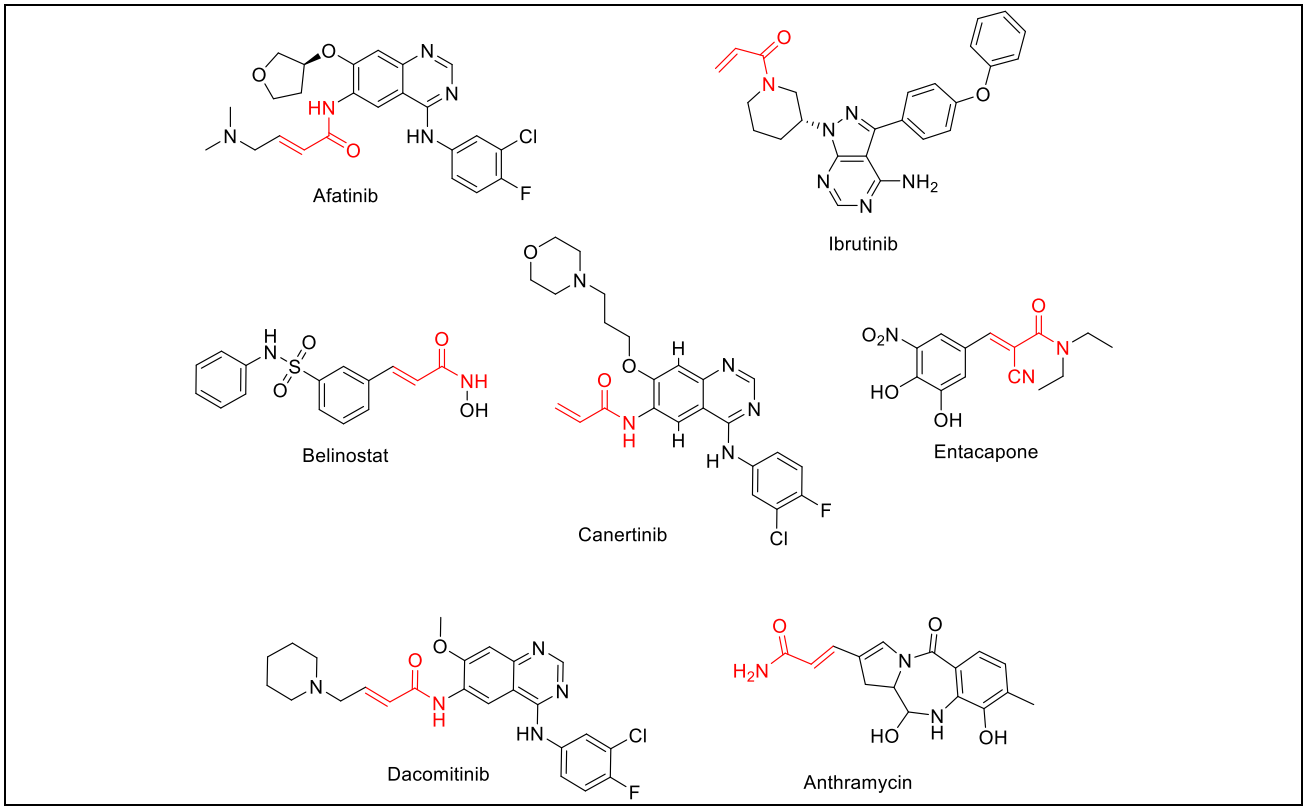
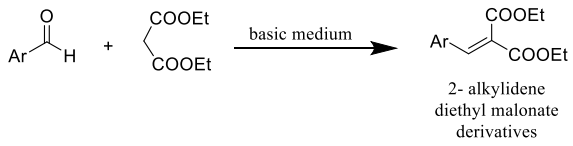
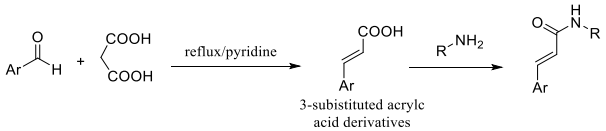


Figure 1. Drugs incorporating acrylamide moiety

refluxing pyridine which promoted what is known as "pyridine-induced decarboxylation" to yield 3-substituted acrylic acid derivatives. The produced acrylic acid derivatives can be further reacted with primary amines to yield 3-substituted acrylamide derivatives[7,14,15] **Scheme 2**.

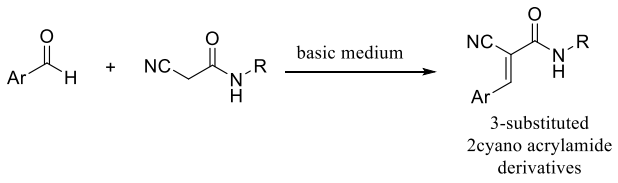


Scheme 1. Knovenagel reaction



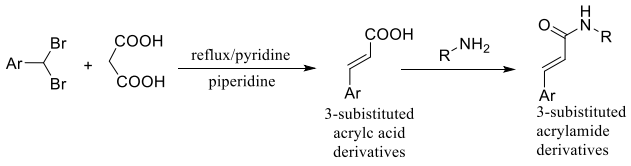
Scheme 2. Knovenagel-Dobner reaction (pyridine induced decarboxylation)

Another applied modification of Knovenagel condensation for synthesis of substituted acrylamides is the reaction of aldehydes with acetamides substituted with an electron withdrawing group at position no. 2 under basic conditions to yield 2,3-disubstituted acrylamide derivatives. The most common is the reaction of the desired aldehyde with *N*-substituted 2-cyanoacetamide derivatives to yield various desired 2-cyanoacrylamide derivatives[1,16–18], **Scheme 3.**



Scheme 3. Knovenagel condensation between aldehydes and *N*-substituted 2-cyanoacetamide derivatives to yield 2-cyanoacrylamide derivatives

Augustine[19] *et al.* reported the synthesis of a series of 3-substituted acrylic acid derivatives with excellent yields using a modification of knovenagel-dobner reaction in which germinal dibromomethylarenes were used as alternatives for non-commercially available aldehydes, the obtained acrylic acid derivatives can be easily converted to the corresponding desired acrylamide derivative via reaction with appropriate primary amine, **Scheme 4**.



Scheme 4. Modified Knovenagel Dobner reaction using germinal dibromomethylarenes as alternative for aldehydes

1.2. Via Horner–Wadsworth–Emmons (HWE) reaction

Applying the principle of HWE reaction[20,21], (E) 3-substituted acrylamide derivatives can be obtained where desired aldehydes or ketones are reacted with acetate esters bearing a phosphonate ester derivative at alpha carbon (2-(phosphonate ester)-acetate ester derivatives) that were previously activated using strong bases as sodium hydride to yield (*E*) 3-substituted acrylate esters. The formed (*E*) 3-substituted acrylate esters undergo either alkaline hydrolysis of ester to give the free acrylic acid followed by reaction with various primary amines to yield the desired 3-substituted acrylamide or direct refluxing the formed 3-substituted acrylate esters with desired primary amine to yield the 3-substituted acrylamide[9,22], **scheme 5**.

1.3. Via Mizoroki-Heck coupling reaction:

The principle of Mizoroki-Heck coupling reaction [23,24] is also applied for synthesis of the 3-substituted acrylamide derivatives. It involves Palladium catalyzed reaction of aryl or aryl halides with acrylic acid esters yielding 3-substituted acrylate esters. The formed 3-substituted acrylate esters undergo both alkaline hydrolysis and reaction of the formed free acid with various primary amines or directly refluxing the formed 3-substituted acrylate esters with desired primary amine to yield the desired 3-substituted acrylamide[25,26], **Scheme 6**.

1.4. Via reaction between 2-cyanoacetamides and aryl isothiocyanates

Another widely applied synthetic methodology is via the reaction between 2-cyanoacetamide derivatives and aryl isothiocyanates under basic conditions to yield a thiolate intermediate which is alkylated using methyl iodide or dimethyl sulfate to yield 3-aryl, 2-cyano, 3-methylthio acrylamide derivatives[27,28], **Scheme 7**.

1.5. Via reaction between 2-cyanoacetamides and carbon disulfide

Reaction of 2-cyanoacetamide derivatives with carbon disulfide under basic conditions yields the dithiolate dianion intermediate which is further alkylated *in-situ* by methyl iodide or dimethyl sulfate to yield 2-cyano-3,3-bis(methylthio)acrylamide derivatives[29,30], **Scheme 8**.

2. Acrylamide reactivity and its functionalization for design of new therapeutic entities

The reactivity of acrylamide moiety has been extensively investigated; it depends mainly on being Michael acceptor. This results from the presence of *α, β*-unsaturated carbonyl where the *α, β*-unsaturated moiety represents the electrophilic center required for Michael addition reaction of various nucleophiles as illustrated in **Figure 2.** This unique property is especially helpful for design of new therapeutic entities where acrylamide moiety can be functionalized for efficient targeting of different proteins which possess nucleophilic residues as cysteine and serine at active drug binding site[31–34].

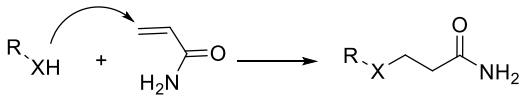


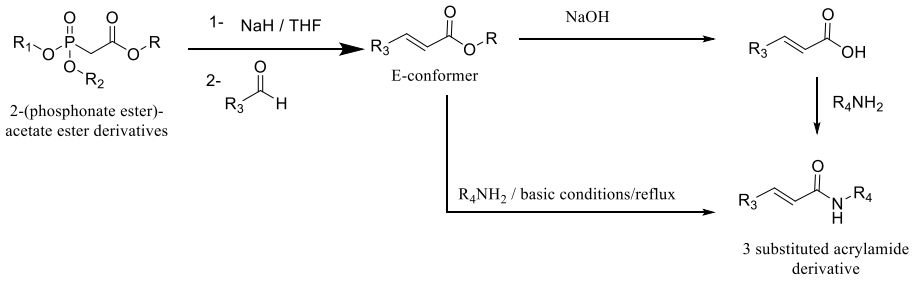
Figure 2. Michael addition to acrylamide

2.1. Advantage of additional nitrile substitution at the alpha carbon

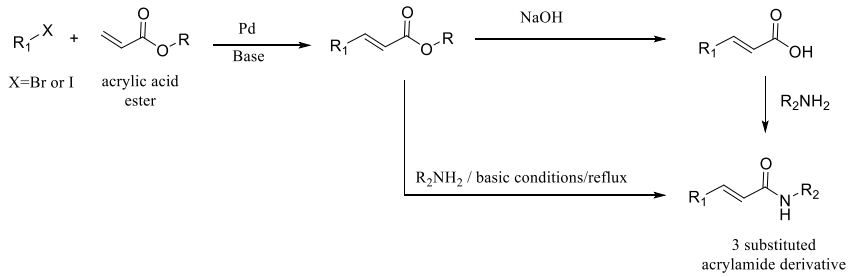
An additional nitrile group at the alpha carbon of acrylamide (2-cyanoacrylamide) can increase the efficiency of acrylamide moiety as a tool for designing successful drugs addressing protein targets rich in nucleophilic residues and H-bond donor residues. This additional group forms “nitrile trap” which traps both nucleophilic residues and H-bond donor residues, for nucleophilic residues it undergoes nucleophilic addition at the electrophilic carbon of nitrile whereas for H-bond donor residues it serves as H-bond acceptor via the lone pair on the nitrogen of nitrile group. The advantage of nitrile moiety as a tool for designing various molecules addressing various therapeutic targets was highlighted by many researchers[35–40].

2.2. Acrylamides a tool for design of targeted covalent inhibitors TCI’s

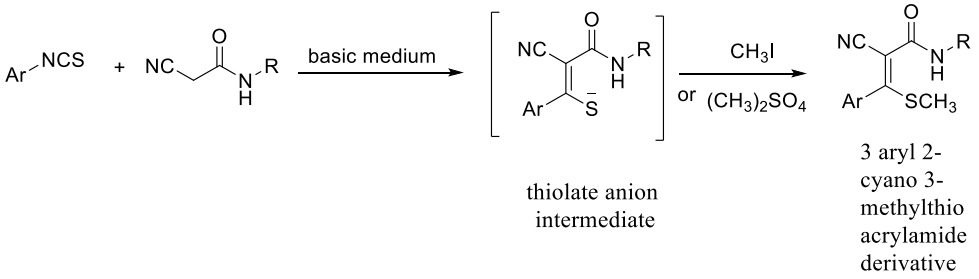
TCI’s are small molecules bearing specific functional groups capable of covalent binding with specific residues at target proteins leading to silencing and inhibition of the protein action. Design of TCI’s is a successful strategy for developing new drugs[40–43], a fact empathized through the well appreciated record of successful drugs belonging to this class of compounds. For example: penicillins and cephalosporins the beta lactam antibiotics exert covalent inhibition to bacterial trans-peptidase enzyme a pivotal for bacterial cell wall synthesis leading to the bactericidal effect.



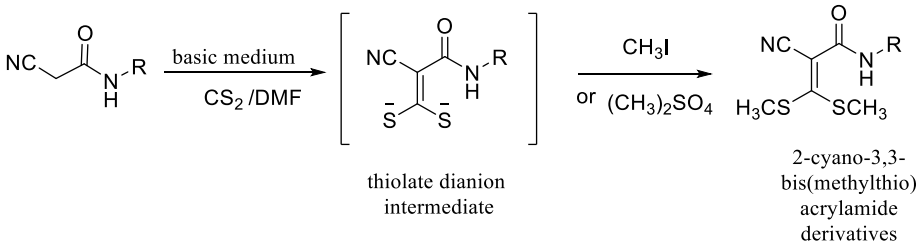
Scheme 5. Horner–Wadsworth–Emmons (HWE) reaction application for synthesis of acrylamides



Scheme 6. Mizoroki-Heck coupling reaction application for synthesis of acrylamides.



Scheme 7. Synthesis of 2-cyanoacrylamide derivatives from aryl isothiocyanates and 2-cyanoacetamide derivatives



Scheme 8. Synthesis of acrylamide derivatives from 2-cyanoacetamide derivatives and carbon disulfide

Another example is the acid catalyzed covalent inhibition of gastric (H^+, K^+)-ATPase by proton pump inhibitors[44]. Additionally Clopidogrel the antiplatelet launched by Sanofi Aventis which exerts its effect via its active metabolite which irreversibly inhibits adenosine diphosphate ADP receptor subtype P2Y12[45]. In the same context Orlistat the gastric lipase inhibitor used for treatment and control of obesity covalently binds to serine residue at the active site of pancreatic and gastric lipases[46]. Various EGFR kinase inhibitors as Afatinib, Carnetinib, Dacomitinib approved for treatment of different types of cancer exert their effect via covalent binding to specific cysteine residue at EGFR active site.

As previously mentioned acrylamide being a Michael acceptor provides an excellent tool for

designing successful TCI's [47,48]. The added value of acrylamide was confirmed by Solca[49] *et al* via x-ray crystallography of Michael addition product of Afatinib an EGFR kinase inhibitor bearing acrylamide moiety and cysteine 797 residue of both wild-type EGFR and mutated $EGFR^{L858R/T790M}$. They also provided experiment based proof that loss of acrylamide moiety leads to loss of activity using an analog lacking the acrylamide moiety. The Michael addition adduct obtained for Afatinib with both the wild EGFR and mutated $EGFR^{L858R/T790M}$ [49] is illustrated in **Figure 3** and **Figure 4** respectively.

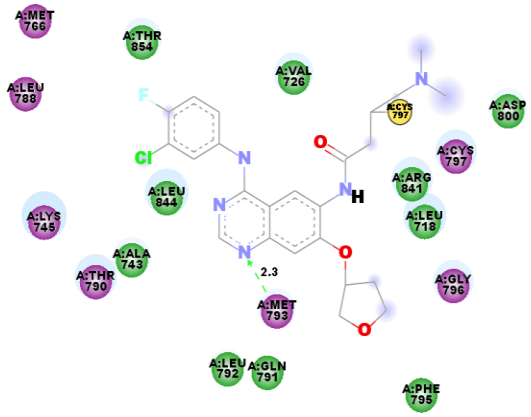


Figure 3. 2D diagram showing covalent interaction of Afatinib with cysteine 797 residue of wild type EGFR[49]

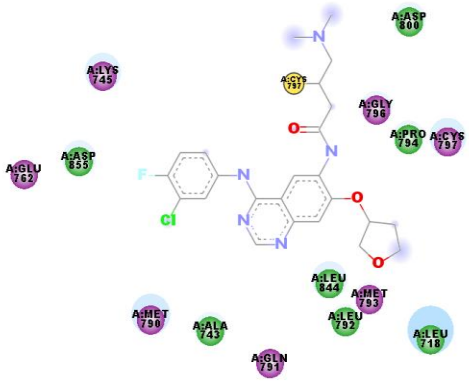
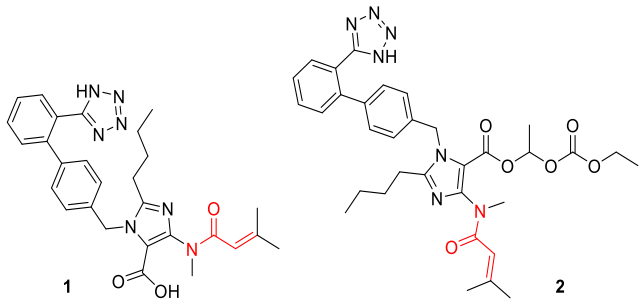


Figure 4. 2D diagram showing covalent interaction of Afatinib with cystiene797 residue of mutated $EGFR^{L858R/T790M}$ [49]

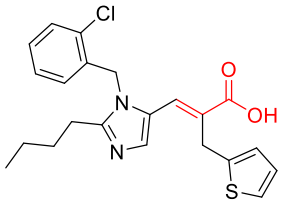
3. Reported biological activities:

3.1. Angiotensin II receptor antagonist activity

Okazaki[11] *et al.* reported the synthesis of a series of imidazole derivatives containing the acrylamide group at position no.4 of the imidazole ring and evaluated them for their angiotensin II receptor antagonist activity. A structure activity relationship study was generated revealing that substitution of imidazole at the 4-position with the *N*-methyl, 3, 3-dimethylacrylamide group resulted in enhanced activity. Compound **1** was superior to the reference drug *in vitro* but with poor *in vivo* activity after oral administration. To overcome this problem prodrug esters were synthesized and evaluated; among which compound **2** (the -[(ethoxycarbonyl)oxy]ethyl ester) exhibited highest *in vivo* activity after oral administration.



Keenan[50] *et al* reported synthesis of a set of substituted (E) - acrylic acid derivatives for evaluation of their activity as angiotensin II receptor. They were guided by a developed pharmacophore model which suggests that the addition of acid chain and an aryl side chain to imidazole mimicking the C-terminal phenylalanine region of native ligand would lead to increased activity. A SAR study was developed which revealed that electron-rich hetero aryl rings improved the activity. Compound **3** was the most potent orally bioavailable candidate.



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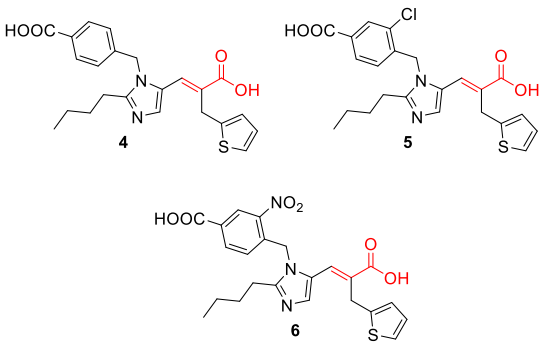
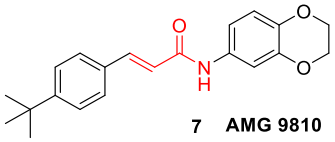
Keenan[51] *et al* resumed their work for developing angiotensin II receptor antagonists where they introduced new modification to mimic the Tyr4 residue of angiotensin II via new para carboxylic group on the N-1-benzyl substitution. This led to evolution of some active compounds at nanomolar concentrations both *in vitro* and *in vivo*, compound **4** the main model for this study exhibited (*in vitro* IC_{50}=1nM and *in vivo* ID_{50}=0.08mg/kg), compound **5** (*in vitro* IC_{50}=1.45 nM and *in vivo* ID_{50}=0.06mg/kg) and compound **6** (*in vitro* IC_{50}=0.15nM and *in vivo* ID_{50}=0.06mg/kg).



3.2. Transient receptor potential vanilloid 1 TRPV1 receptor antagonist

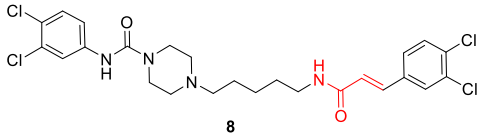
Gavva[52] *et al*. reported the evaluation of compound **7** coded as **AMG 9810** for vanilloid receptor 1(VR1) –also known as transient receptor potential vanilloid 1 TRPV1- antagonist activity. VR1 is a cation channel receptor bound to the membrane of peripheral sensory neurons. Antagonism of VR1 produces antihyperalgesic effect in neuropathic and inflammatory pain animal models[53]. **AMG9810** blocked TRPV1 activation in all models of TRPV1 activation at nanomolar concentrations (IC_{50} range 15.8-294 nM for different models).



7 AMG 9810

3.3. Antidiabetic activity

Li[54] *et al* reported discovery of set of 3-phenyl acrylamide derivatives developed at GlaxoSmithKline GSK as novel potent human liver glycogen phosphorylase a (HLGPa) inhibitors via high-throughput screening. The discovered compounds possess an extreme advantage of being glucose-sensitive where they exhibited activity at high blood glucose levels and no or minimal activity when blood glucose level decreases. The most active compounds were compound **8** (IC_{50} 0.94 µM) and compound **9** (IC_{50} 0.17 µM).



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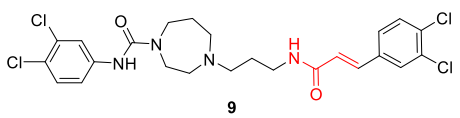

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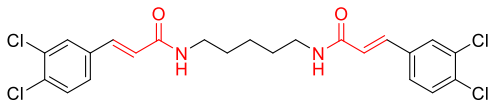
Onda[6] *et al* reported synthesis of a series of 3-(3,4-dichlorophenyl)acrylamide derivatives and their evaluation for human liver glycogen phosphorylase A (HLGPa) inhibitory activity. Compound **10** was most active (IC_{50} 0.023 µM). X-ray crystallography study of the enzyme complexed with compound **10** revealed that compound 10 exhibited hydrophobic interaction with the enzyme via the 3,4-dichlorophenyl moiety.



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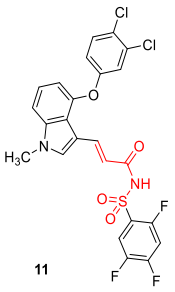
3.4. Prostaglandin E_2 receptor-3 EP3 antagonist activity

3-Acrylsulfonamide-4-aryloxy indole series was synthesized and evaluated for prostaglandin E_2 receptor-3 EP3 antagonist activity by Zhou[5] *et al*. EP3 is associated with prostaglandin E_2 induced platelet aggregation[55], thus EP3 antagonism would produce antiplatelet activity without inhibiting PGE_2 production which is a main drawback of conventional treatments. Synthesized derivatives were evaluated for IC_{50} of human EP3 receptor binding among which compounds **11**, **12** and **13** showed highest potency with IC_{50} of 2.6 nM, 3.5 nM and 4.6 nM; respectively.



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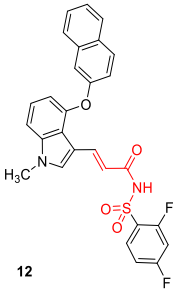

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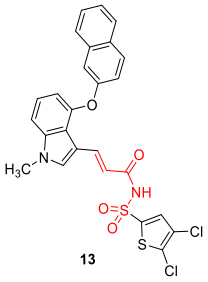

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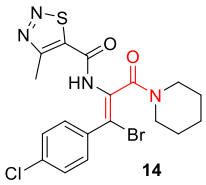
3.5. Antiviral activity

3.5.1. Antiviral activity against hepatitis B virus HBV

Dong[56] *et al.* reported the design, synthesis of a novel series of acrylamide derivatives bearing 1,2,3-thiadiazole heterocycle and their evaluation for their *in vitro* antiviral activity against HBV. The IC_{50} values for the inhibition of HBV DNA replication exhibited by most potent compounds **14** and **15** were 3.59 µg/mL and 10.4 µg /mL respectively. These results are very promising taking into consideration that the IC_{50} exhibited by the positive control lamivudine was14.8 mg/mL.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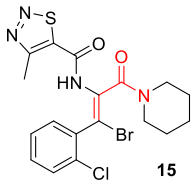
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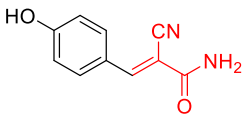
3.5.2. Dengue DEN and West Nile virus WNV protease inhibitory antiviral activity

Christoph[3] *et al.* reported the synthesis of a set of 86 analogues bearing 3-aryl, 2-cyanoacrylamide scaffold and their evaluation for serine proteases (NS2B-NS3) inhibitory activity for both DEN and WNV. Compound **16** which possess *para* hydroxy substitution at aryl ring was the most potent with a K_i value for Dengue virus protease of 35.7 µM and 44.6 µM for West Nile virus proteases respectively. The target selectivity for viral proteases versus thrombin was 2.8:1 for DEN protease and 2.3:1 for WNV protease. The mechanism of inhibition is via covalent irreversible inhibition by targeting the serine residue of target enzymes.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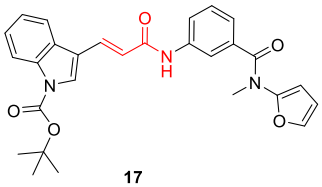
3.6. Diacyl glycerol transferase DGAT inhibitor activity

Hepatic DGAT represents a potential target for treatment of obesity and fatty liver disorders[57]. lee[58] *et al* reported synthesis of series of indolyl acrylamides and evaluation for their DGAT inhibitory activity. Compound **17** exhibited highest potency with IC_{50} of 2.5µM inhibiting synthesis of triglyceride in dose dependent manner. The study revealed the selectivity of indolyl acrylamides against DGAT-2.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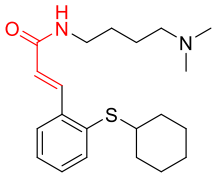
3.7. Soluble guanylyl cyclase sGC activator activity

sGC is an enzyme responsible for cellular conversion of guanosine triphosphate (GTP) into cyclic guanosine mono phosphate cGMP. It serves as a receptor for nitric oxide (NO) and cellular transduction pathway for physiological NO induced vasodilator effects. sGC activators are identified as targets for novel vasodilator drugs. Zhang[9] *et al* reported the synthesis of set of *O*- substituted 3-aryl acrylamides. Synthesized compounds exhibited EC_{50} ranging (2.9-100 µM) compound **18** was the most active with EC_{50} 2.9 µM.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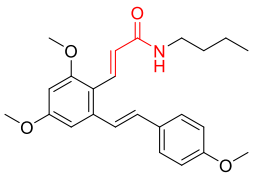
3.8. COX II inhibitor activity

Yao[59] *et al* reported the synthesis of series of novel resveratrol amides including acrylamide derivatives and evaluation of their cyclooxygenase-2 (COX-2) inhibitory activity. Among various amides acrylamide derivatives showed the highest activity. Compounds **19** and **20** exhibited the most potent COX-2 inhibitory activity with the IC_{50} values of 1.02 and 1.98 µM, respectively. Molecular docking studies were carried out for **20** and **21** into COX-2 active site revealing the interaction via strong hydrophobic interactions and hydrogen bonding.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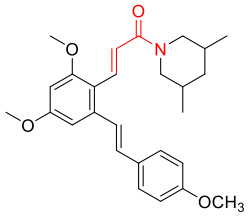
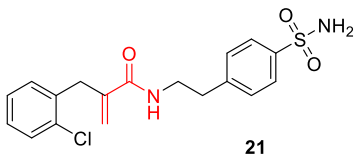

20

3.9. NLRP3 inflammasome inhibitor activity

NLRP3 inflammasome is an oligoprotein complex coded by NLRP3 gene, thus nominated after it. It is expressed mainly in myeloid tissue and macrophages as a part of innate immunity. It is involved in inflammatory response to different pathogens and inflammatory situations. Its role involves a caspase-1 activity for activation of chemokines as IL-1β and induction of chemotaxis, as well as roles in induction of necrosis and pyroptotic cell death[60]. Aberrations of NLRP3 inflammasome activity have been linked to number of diseases as neurological disorders[61], Alzheimer's disease[62], auto-immune disorders[63] and inflammatory disorders[64].

Cocco[65] *et al.* reported synthesis of a set of acrylamide derivatives and evaluation for their activity as NLRP3 inflammasome inhibitors, including assay for inhibition of I IL-1β release from macrophages including mutant subtypes, then the most active compounds were further evaluated for NLRP3 ATPase

activity. Compound **21** was the most active ,it inhibited the NLRP3 ATPase activity in concentration dependent manner with IC_{50} of 74 µM , it was further evaluated for binding mode and ligand interaction with ATP binding pocket of ATPase activity domain of NLRP3 inflammasome via computational docking study which proposed a covalent interaction with cysteine 419 residue , hydrogen bond between tyrosine 381 and oxygen of carbonyl group, whereas the phenyl sulfonamide group exhibited hydrogen bonding and charge-transfer interactions with lysine 232, threonine 233, arginine 237, and histidine 522.

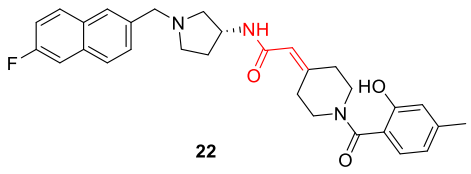


21

3.10. Chemokine receptor 3 CCR3 antagonist activity

CCR3 is a receptor for inflammatory chemokines as eaotaxin, MCP (monocyte chemo-attractant protein) and RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted), it is expressed mainly on eosinophils[66]. It is involved in the chemotaxis of eosinophils in different inflammatory and allergic diseases thus represents potential target for addressing inflammatory and allergic diseases[67].

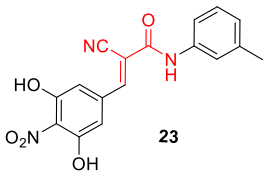
Sato[4] *et al.* reported synthesis and characterization of acrylamide derivatives with potent CCR3 inhibitory activity and evaluation of *in vitro* metabolic stability in human liver microsomes expressed as clearance rate (CL_{int}; mL/min/kg) of these compounds. A SAR study was generated for both CCR3 antagonism activity and CL_{int} values .compound **22** was among potent inhibitors (IC_{50} = 8.4 nM) with highest metabolic stability (Cl_{int} <64 mL/min/kg).



22

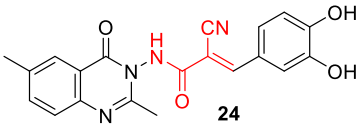
3.11. Antitumor activity:

Zhou *et al.* reported synthesis of a set of 3-aryl, 2-cyanoacrylamide derivatives and evaluation of their anti-tumor activity against human nasopharyngeal carcinoma cell line KB, human gastric carcinoma cell line BGC-823 and human hepatoma cell line BEL-7402. Compound **23** was the most potent with IC_{50} values of 5.6 µg/mL for human gastric carcinoma cell line BGC-823, 13.1 µg/mL for human nasopharyngeal carcinoma cell line KB and 12.5 µg/mL for human hepatoma cell line BEL-7402.



23

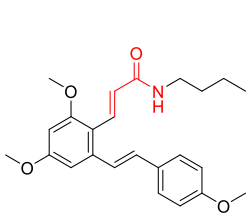
Alafeefy[68] *et al* reported synthesis of a series of substituted quinazolin-4-(3*H*)-one-tyrophostin derivatives and evaluated their antitumor activity against selected tumor cell lines. Evaluation included human cervical cancer cell line (HeLa), human hepatocellular liver carcinoma cell line (HepG2) and human breast cancer cell line MCF-7. The design was based on combining the inherent antitumor activity of tyrophostin with selected quinazolines. Among evaluated compounds 10 of them exhibited considerable activity against the tested cell lines with the IC_{50} values range 0.008-0.015 µM. Compound **24** was the most potent with IC_{50} of 0.008 µM against all tested cancer cell lines.



24

Resveratrol is a phytoalexin phenolic compound produced by several plants. It is reported to have biological activity as antimicrobial, antitumor, and inducer of apoptosis for tumor cells [69,70].

Yao[59] *et al* reported synthesis of different series of novel resveratrol amide derivatives involving acrylamide derivatives and evaluated their anti-tumor activity against breast cancer MCF-7, non-small cell lung cancer cell line A549 and melanoma cancer cell line B16-F10. Compounds **25, 26** and **27** exhibited most potent anti-proliferative activity against selected cancer cell lines with IC_{50} values range of 1.33-3.26 µg/ml.



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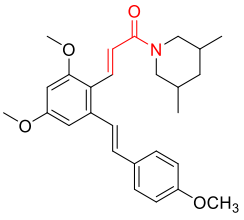

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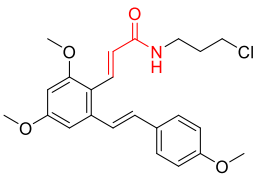
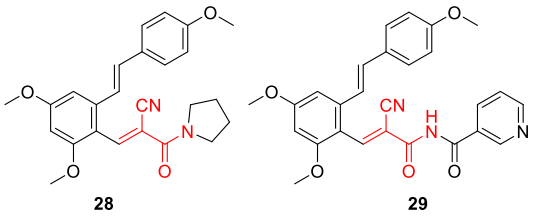
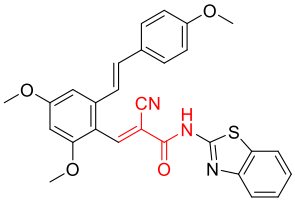


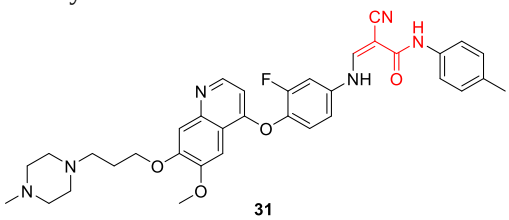
27

Ruan[71] *et al* reported synthesis of another series of 3-resveratrol, 2-cyno acrylamide derivatives and evaluated their activity against selected cancer cell lines including human hepatoma HuH-7, chronic myelocytic leukemia cell line K562, and lung carcinoma cell line A549. The most active compound against HuH-7 was compound **28** with IC_{50} of 4.5 µmol/L. the most active compound against K562 was compound **29** with IC_{50} of 2.9 µmol/L and the most active compound against A549 was compound **30** with IC_{50} of 3.8 µmol/L.





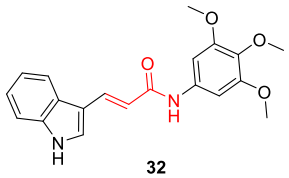
Hu[72] *et al* reported synthesis of series of 4-phenoxyquinoline derivatives incorporating 3-amino, 2-cyano-acrylamide derivatives and their evaluation against five cancer cell lines which are: human colorectal adenocarcinoma HT-29, non-small cell lung cancer H460, pulmonary adenocarcinoma A549, gastric cancer cell line MKN-45 and glioma cell line U87MG. The tested compounds were compared to Foretinib as reference. A SAR study was generated indicating that the compounds with methyl groups at 4-position of the *N*-phenyl acrylamide are more effective. Compound **31** was most potent with IC_{50} of 0.04 µM/L, 0.09 µM/L, 0.67 µM/L, 0.39 µM/L and 1.10 µM/L against HT-29, H460, A549, MKN-45 and U87MG cell lines; respectively.



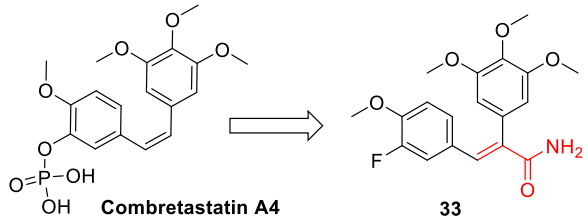
3.11.1. Tubulin polymerase inhibition activity

Tubulin polymerase enzyme is an essential enzyme for synthesis of microtubules a crucial cellular protein for mitotic division, thus it represents valuable target for development of antitumor agents.

Baytas[7] *et al* reported characterization of series of trans-indole-3-acrylamide derivatives as structural analogues to colchicine a well-known tubulin polymerase inhibitor[73] and evaluation of their antitumor activity against selected five human cancer cell lines (cervical cancer cell line HeLa, breast cancer cell line MCF7, breast cancer cell line MDA- MB-231, B-cell lymphoma cell line Raji and leukemia cell line HL-60). The results showed no significant effects on MDA-MB-231, MCF7 and HeLa. Compound **32** exerted inhibitory activities against Raji and HL-60 cell lines with IC_{50} values of 9.5 and 5.1 µM; respectively. It also exhibited moderate inhibitory activity on tubulin polymerization (IC_{50} value 17 µM in tubulin polymerase inhibitory assay). Cell cycle analysis showed arrest of cells at G2/M phase in HL-60. Moreover, compound **32** induced apoptotic cell death through the activation of caspase-3. Molecular modeling simulation study suggested that compound **32** binds to the colchicine site of tubulin.



Borrel[74] *et al.* reported synthesis of series of derivatives of combretastatin A4 a well-defined tubulin polymerase inhibitor[75]. The new derivatives included acrylamide derivatives and evaluated their cytotoxic effects against IGROV, KB-3-1 and MCF-7cancer cell lines. Tubulin polymerization inhibitory activity was also evaluated. Potent inhibitory activity was observed for acrylamide derivatives. Compound **33** the most potent cytotoxic agent exhibited activity against tubulin polymerase with an IC_{50} 1.5 fold IC_{50} of colchicine.

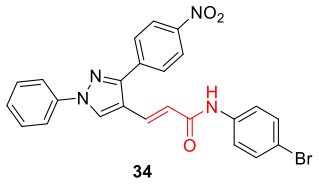


3.11.2. HDAC inhibitor activity

Histones are the nuclear proteins responsible for packing DNA into nucleosome complex. The regulation of almost all cellular activities starts by activation of specific nucleosomes via acetylation and deacetylation of the lysine residue of histone. The process of acetylation and deacetylation is catalyzed by family of enzymes known as histone deacetylases.

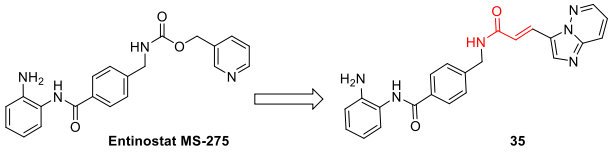
Through its acetylation and deacetylation activity HDAC regulates various cellular activities [76], aberrations of HDAC have been linked to number of diseases including various types of cancer[77].

Li[15] *et al.* reported the design and synthesis of series *N*-phenyl acrylamide derivatives and evaluated their cytotoxic activity against colon cancer cell line HCT 116 and HDAC-1 inhibitory activity. Compound **34** was the most active with IC_{50} of 0.62 µM against HCT116 colon cancer cell line and IC_{50} of 0.42 µM for HDAC-1 inhibitory activity.



34

Li[78] *et al.* reported synthesis of novel acrylamide analogues for Entinostat MS-275 an established HDAC-1 inhibitor[79] applying principles of non-classical isosterism. All synthesized compounds were evaluated for HDAC inhibitory activity and cytotoxic activity against colon cancer cell line HCT 116, breast cancer cell line MCF-7 and pulmonary adenocarcinoma cell line A549. All compounds exhibited superior antitumor effect. Compound 34 was most potent with IC_{50} of 0.118 µM, 1.258 µM, 2.871 µM and 0.723 µM for HDAC-1 inhibitory assay; cytotoxicity assay for HCT-116, MCF-7 and A549 cancer cell lines; respectively. Assay of pharmacokinetic profile was conducted for compound **35** which showed bioavailability of 76% in rat model.



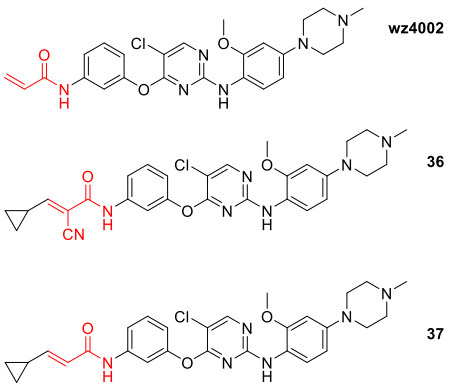
3.11.3. Protein kinase inhibitor activity

Protein kinases represent a huge family of cellular enzymes which are pivotal in signal transduction pathways that control numerous cellular functions, including proliferation, differentiation, migration, apoptosis, and angiogenesis[80]. protein kinase enzymes represent a potential target for TCI's as a result of the high density of nucleophilic residues at active sites of protein kinases. As formerly mentioned numerous approved drugs with protein kinase inhibitory activity incorporate acrylamide moiety. In continuation for this promising activity several research papers reported the activity of different acrylamide derivatives against different kinases.

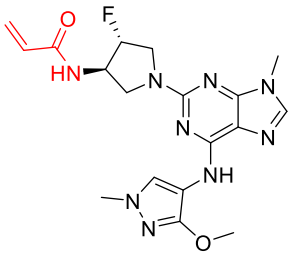
3.11.3.1. EGFR kinase inhibitory activity

EGFR is a transmembrane receptor tyrosine kinase which plays central role in cell adhesion, migration proliferation and differentiation via different signal transduction pathways[81]. Up-regulated EGFR signaling has been linked to a variety of tumor progression to metastasis and invasion; thus EGFR is a potential target for treatment of cancer[82]. Mutations in EGRF has been reported to be linked to resistance to conventional 1st generation EGFR kinase inhibitors as gefitinib causing serious relapse of therapy. For instance exon 19 deletion mutation (labeled $EGFR^{Del}$), substitution mutation L858R (labeled as $EGFR^{L858R}$), substitution mutation T790M (labeled as $EGFR^{T790M}$), mutation including both double exon 19 deletion and T790M (labeled as EGFR $^{T790M/Del}$) and mutations involving both L858R and T790M (labeled as $EGFR^{L858R/T790M}$) arouse which required development of more potent generations[83].

Rauh[82] *et al.* reported the design, synthesis and evaluation of novel EGFR kinase inhibitors targeting mutant types of EGFR kinase. The design was based on the scaffold of WZ4002 a third generation EGFR kinase inhibitor exhibiting high potency against Mutant EGFR kinases EGFR ^{L858R} and EGFR ^{T790M} [83]. The designed analogues included modification of WZ4002 structure by introducing certain substitutions at positions no.2 and 3 of the terminal acrylamide. In position no.2 they introduced cyano and trifluoromethyl electron withdrawing groups. In position no.3 they introduced different aliphatic and aromatic groups. Based on the obtained IC_{50} values a SAR study was generated. The 2-cyano derivatives exhibited much higher activity than the corresponding 2-triflouromethyl analogues; this was attributed to steric repulsions of the bulkier trifluoromethyl group with Arg841 of EGFR kinase. The designed derivatives were highly selective for the mutant types while much less active towards the wild type EGFR a property which WZ4002 lacks. Compound **36** the most active 2-cyanoacrylamide analogue inhibited $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$ with IC_{50} of 0.35 µM and 0.083 µM; respectively. The IC_{50} of compound **36** for wild type EGFR was >10 µM compared to IC_{50} of 0.016 µM for WZ4002 which empathize greater selectivity of designed compounds for mutant types. To assess the contribution of nitrile group the activity of compound **37** an analogue of compound **36** lacking 2-cyano group was evaluated. It exhibited IC_{50} of 2.8 µM (8 folds) and 0.83 µM (10 folds) for $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$ respectively, which asserts the importance of the 2-cyano group for development of more potent candidates.



Behenna[84] *et al* reported the structure based design, synthesis and biological evaluation of the purine derivative (PF-06747775) which exhibited high selectivity and affinity towards four types of mutant EGFR kinases over wild type EGFR including EGFR exon 19 deletion mutation $EGFR^{Del}$, substitution mutation $EGFR^{L858R}$, double mutation $EGFR^{T790M/L858R}$ and double mutation EGFR T790M/exon 19 deletion $EGFR^{T790M/Del}$, exhibiting nanomolar IC_{50} of 5 nM, 4nM, 12nM and 3nM respectively whereas its IC_{50} for wild type EGFR was 307nM. PF-06747775 is currently in phase I clinical trials.



PF-06747775

3.11.3.2. BTK inhibitor activity

BTK is a non-receptor tyrosine kinase expressed in hematopoietic B cells. BTK controls various signal transduction pathways of B cells. Dysregulation of BTK was linked to number of B cell malignancies[80]. Ibrutinib a purine analogue bearing a terminal acrylamide moiety was the 1st BTK inhibitor approved by FDA in 2013 for treatment of mantle cell lymphoma.

Wang[85] *et al* reported the synthesis of a series of *N*,9-diphenyl-9*H*-purin-2-amine derivatives and evaluated their BTK inhibitor activity as well as cytotoxic activity against Ramos and Raji B cell leukemia cell lines both of which is characterized by high expression of BTK. Compound **38** was the most potent among the designed analogues. It was almost equipotent to the control Ibrutinib. It exhibited IC_{50} values of 0.4nM, 7.75µM, 12.6 µM for BTK inhibition, Ramos and Raji leukemia cancer cell lines; respectively. Whereas for Ibrutinib the IC_{50} values were 0.3 nM, 8.11 µM and 15.2 µM; respectively.

3.11.3.3. Janus kinase III JAK 3 inhibitor

Janus kinases (JAKs) are cytoplasmic tyrosine kinases that play central role regarding cytokines signaling in immune cells. Considering these facts JAKs arise as potential targets for development of new anti-inflammatory or immunosuppressant drugs [86].

Forster[87] *et al* reported the synthesis of series of novel 2-cyanoacrylamide derivatives and their evaluation as selective JAK3 inhibitors. X-ray crystallography was performed which provided precise data regarding identification of the binding pocket and types of interaction. Among synthesized compounds compound **39** and **40** were the most potent JAK3 inhibitors with nanomolar IC_{50} values of 9 nM and 17 nM for **39** and **40**; respectively. Moreover, the x-ray crystallography for JAK3 bound to both **39** (PDB ID 5LWM) and **40** (PDB ID 5LWN) revealed covalent modification of cysteine 909 residue and hydrogen bonding interaction of 2-cyano group with arginine 911 residue **Figure 5**.

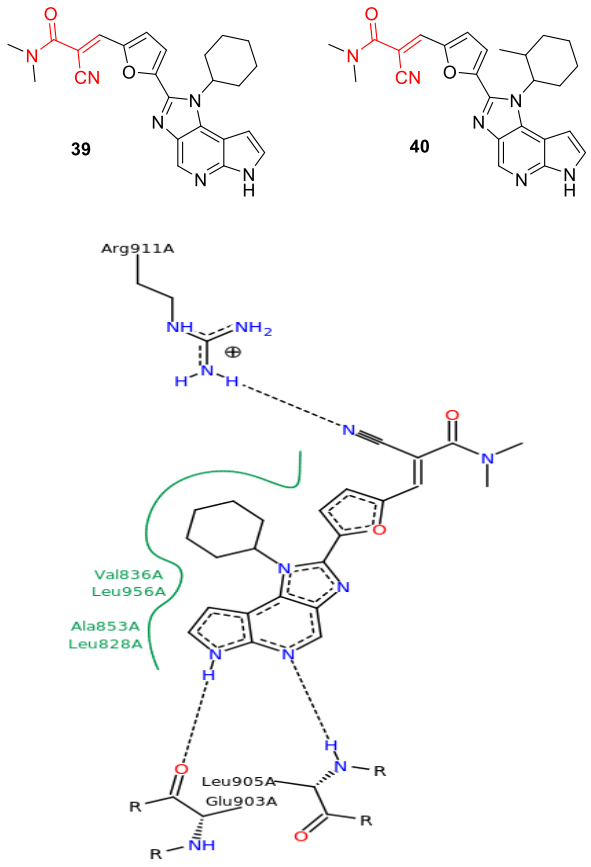
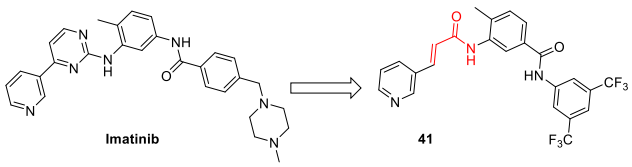


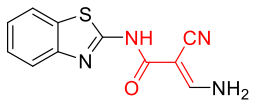
Figure 5. Hydrogen bonding & hydrophobic interactions between JAK3 residues & compound 39



3.11.3.4. Inhibitor of BCR–ABL kinase

BCR-ABL Kinase is a mutated membrane tyrosine kinase resulting from a translocation mutation between ABL gene on chromosome 9 and BCR gene on chromosome 22 in myeloid cells; this translocation resulted in a new fusion mutation known as BCR-ABL mutation[88]. The non-mutated ABL gene codes for normal functioning membrane tyrosine kinase involved in mitotic pathway. Under physiologic conditions the function of ABL coded tyrosine kinase is regulated and controlled, whereas the mutated BCR–ABL kinase is unregulated and act in an always-on mode leading to uncontrolled cell division. BCR-ABL kinase mutation as associated with chronic myeloid leukemia[88].

Applying principles of nonclassical electronic isosteres Li[25] *et al*. reported synthesis of series of acrylamide derivatives as analogues for Imatinib and Nilotinib and evaluation of their cytotoxic activity on K562 leukemia cancer cells *in vitro* as well as inhibitory effect on BCR–ABL kinase. Results revealed that compounds with trifluoromethyl substitution were the most active. Compound **41** was the most promising exhibiting IC_{50} of 20.6 nM for BCR–ABL kinase inhibition assay lower by 10.5 fold than that for imatinib and IC_{50} of 32.3 nM for cytotoxic activity which is 12 folds lower than that of imatinib.



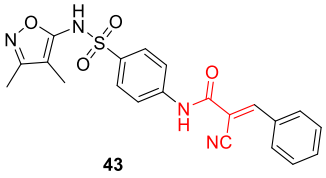
42

3.12. Antimicrobial activity

Regarding antimicrobial activity several research papers reported the synthesis and evaluation of antimicrobial activity of various compounds incorporating acrylamide derivatives.

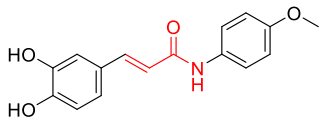
Bondok[18] *et al* reported synthesis of compound **42** a 2-cyanoacrylamide derivative incorporating benzothiazole moiety. It exhibited a good antimicrobial activity against tested strains with MIC of 25 µg/ml against Gram-negative *E. coli*, 50 µg/ml against Gram positive *B. thuringiensis* and 12.5 µg/ml against *Botrytis fabae* fungal strain

Nasr[89] *et al.* reported the synthesis of compound **43** a 2-cyanoacrylamide derivative bearing sulfisoxazole moiety which exhibited good antimicrobial activity against tested strains with MIC of 7.81 µg/ml, 1.95 µg/ml and 3.9 µg/ml against Gram positive bacteria *S. pneumoniae*, *B. subtilis* and *S. epidermidis*; respectively and MIC of 1.95 µg/ml,7.81 µg/ml and 0.49 µg/ml against Gram negative bacteria *E. coli*, *P. vulgaris* and *K. pneumonia;* respectively.



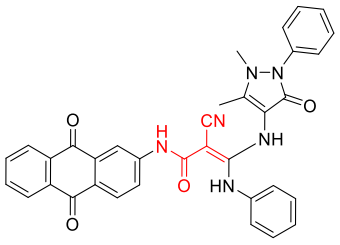
43

Fu[8] *et al.* reported synthesis of a set of acrylamide derivatives and evaluation of their antimicrobial activity. Compound **44** was the most potent with MIC of 3.12 µg/ml against gram-positive bacteria *Bacillus subtilis*, 50 µg/ml against gram-negative bacteria *P. fluorescens*, and 42.8 µg/ml against fungal strain *C. albicans*.



44

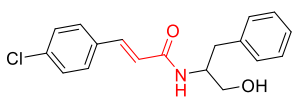
Gouda[27] *et al* reported the synthesis of set of anthraquinone derivatives incorporating 2-cyanoacrylamide derivatives and evaluation of their antimicrobial activity against selected strains using diameter of zone of inhibition in mm as indication for potency. Among synthesized compounds compound **45** was the most active with inhibition zone of 19 mm. for Gram positive *S. epidermidis*, 27 mm. for Gram negative *P. aeruginosa*, 18 mm. and 13 mm. for fungal strains *A. solani* and *F. solani*; respectively.



45

3.13. Anti-mycobacterial activity

Avalos[90] *et al*. reported synthesis of set of α,β-unsaturated amides and evaluation of their anti-mycobacterial activity against two *Mycobacterium tuberculosis* strains which are sensitive strain H37Rv and a resistant clinical isolate. Compounds **46** and **47** were the most potent acrylamide derivatives, they exhibited MIC of 2 µg/ml and 16 µg/ml against sensitive and resistant strains; respectively.



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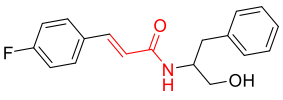

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CONCLUSION

In this article we have provided an updated review describing the advances in medicinal chemistry applications of acrylamide derivatives highlighting the various synthetic pathways, the chemical reactivity of acrylamide derivatives, how it can be functionalized for design of new drugs and the spectrum of reported biological activities and applications.

Conflict of Interest

The authors declare that they don't have any conflict of interest.

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