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Hands-on Synthetic Approaches and Biological Activities of Anthranilic Acid Derivatives: A mini-review

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Abstract

Anthranilic acid scaffold is a pivotal class of amino organic acids used for the construction of many organic candidates exhibiting a wide range of industrial, pharmaceutical, and biological activities. In addition, anthranilic acid derivatives are considered a cheap and efficient stating precursor for the production and synthesis of various marketed available drugs like furosemide (diuretic), tranilast (antiallergic), betrixaban (anticoagulant) and analgesic & anti-inflammatory fenamates. Furthermore, numerous anthranilic acid analogs with potential anticancer, antimicrobial, insecticidal, antiviral, anti-inflammatory activities and other biological activities have been disclosed over the last thirty years. The current review represents a brief and simple summary of different synthetic methodologies and techniques applied for the construction and synthesis of different anthranilic acid analogs and derivatives along with a concise discussion of the potential therapeutic activity of these synthesized derivatives.

Keywords: Ullmann-Goldberg; ultrasonic irradiation; microwave irradiation; anticancer; Human aldo-keto reductase; HCV-NS5B; nuclear farnesoid x receptor.

1. Introduction

Anthranilic acid, 2-aminobenzoic acid (AA) and its derivatives **(Figure 1)** are considered multipurpose and economical precursors for the synthesis of many organic compounds and commercialized drugs that show a diverse range of pharmaceutical and biochemical activities. AA is also involved in the biosynthesis of many amino acids like tryptophan and its derivatives[1]. According to the literature, numerous reported AA derivatives display a diverse spectrum of biological and medicinal activities such as anticancer[2], antimicrobial[3], insecticidal[4], antiviral[5] and anti-inflammatory activities[6]. There are many examples for marketed available drugs containing AA scaffold (**Figure 2**). The diverse and interesting biological profile of AAs inspires the researchers to synthesize many novel series of compounds bearing AA moiety using different synthetic techniques and investigate their potential biological activity. The present review briefly highlights the different classical and advanced synthetic approaches used for the synthesis of various AA derivatives along with some examples of different biological activities of these synthesized analogs.

2. Synthesis of anthranilic acids.

2.1. General approaches.

The industrial synthesis of AA is achieved through the oxidation of o-xylene **15** to produce phthalic anhydride **16** which is converted to phthalimide **17** through addition of ammonia. Then phthalimide is subjected to Hofmann rearrangement *via* reacting with sodium hypochlorite under basic conditions to afford AA **1** (**Figure 3**) [1,7].

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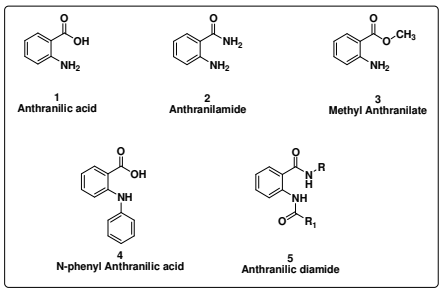

Figure 1: Structure of AA and some of its analogs

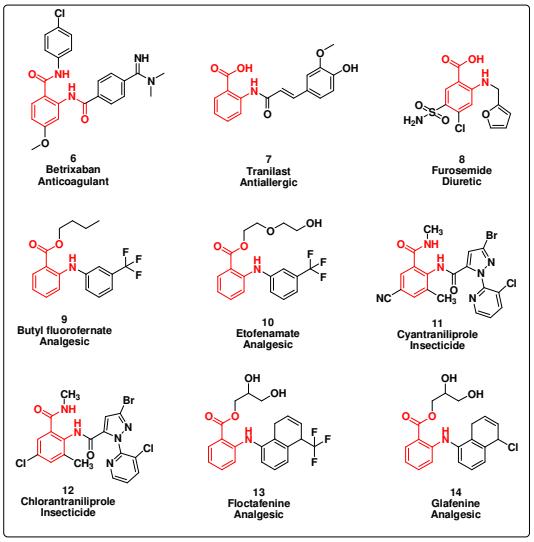

Figure 2: Representative examples of commercially available drugs containing AA scaffold

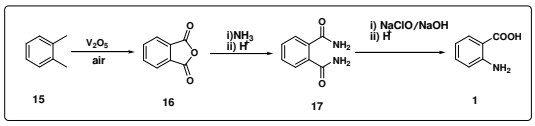

Figure 3: Industrial preparation of AA

Ring substituted AAs **19** are constructed through the reaction of the corresponding isatins **18** with sodium hydroxide and hydrogen peroxide (**Figure 4**). This methodology is tolerable for alkyl, halo and nitro isatins[8].

2.2. Metal-catalyzed C-N bond formation reaction.

2.2.1. Copper-catalyzed coupling reaction.

N-aryl-AAs were firstly described through the copper-catalyzed Ullmann-Goldberg coupling reaction. This reaction is based on the reaction of halobenzoic acids **20** with alkyl- or aryl-amines **21**, or conversely, the reaction of AA derivatives with aryl halides **23** using copper (metal, oxide, or salt) as a catalyst to produce N-phenyl AA analogs (**Figure 5**) [9,10]. To overcome the drastic reaction conditions (long reaction times and high temperatures), numerous modifications were proceeded on this coupling methodology utilizing a broader range of halobenzoic acid substrates, aryl amines and anilines along with using a multiple types of bases and copper & copper complexes [11-17].

In 2006, wolf and co-workers reported an approach for the synthesis of *N*-alkyl and *N*-aryl AAs **26** in high yields and without need of acid protection via regioselective copper-catalyzed amination of bromobenzoic acids **24** with different aromatic and aliphatic amines **25** (**Figure 6**) [18,19].

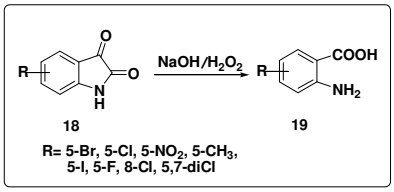

Figure 4: Synthesis of AA derivatives form their corresponding isatines

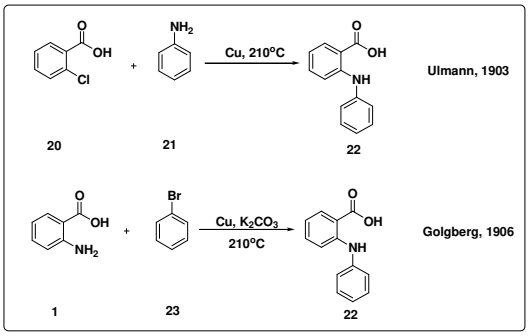

Figure 5: Ullmann-Goldberg coupling reaction for the preparation of *N*-phenyl AA

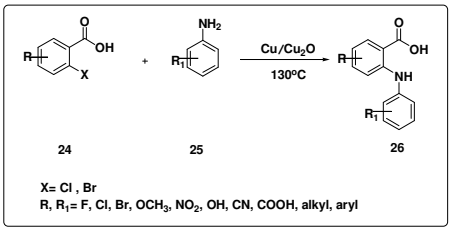

Figure 6: Synthesis of *N*-alkyl and *N*-aryl AAs reported by Wolf *et al.*

2.2.1.1. Advanced copper-catalyzed coupling reaction.

2.2.1.1.1. Ultrasonic irradiation.

Many advanced methodologies like ultrasonic and microwave irradiation (MW) have been accomplished to enhance and accelerate the Ullmann-

Goldberg coupling reactions. Hanoun *et al* reported the synthesis of various *N*- aryl AA derivatives **29** through copper-catalyzed coupling of 2-halogenobenzoic acids **27** with aromatic amines **28** using ultrasonic irradiation instead of classical heating methodology[20]. Later, Robin and co-workers published a similar approach for the synthesis of *N*-aryl AAs showing imidazolo, cyclopent, dioxolo, and dioxino supplementary ring systems. This synthetic approach showed higher product yield and shorter reaction time than the classical coupling reaction(**Figure 7**) [21].

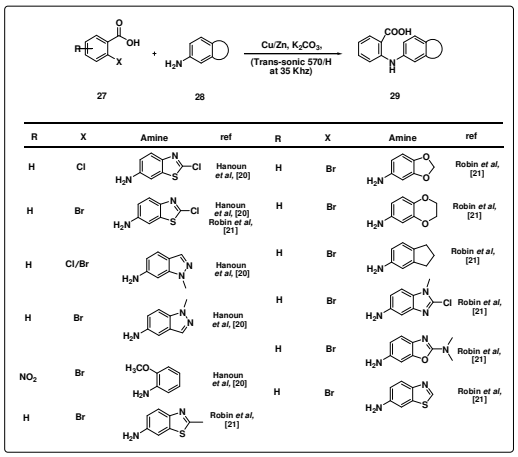

Figure 7: Copper-catalyzed Ullmann-Goldberg coupling of 2-substituted halogenobenzoic acids with aromatic amines using ultrasound irradiation technique

In 2003, Comdom and co-worker also used ultrasonic irradiation for the construction of *N*-phenyl AAs **32** in high yields and short reaction time via copper-catalyzed Ullmann-Goldberg coupling reaction using water as a solvent(**Figure 8**) [22].

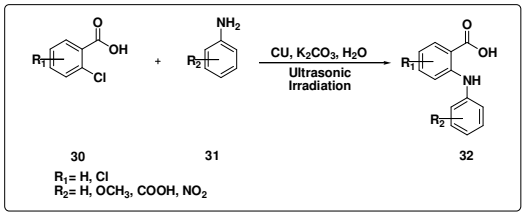

Figure 8: Synthesis of *N*-Phenyl AA derivatives disclosed by Comdom *et al.*

In 2007, Docampo and co-workers reported one-pot synthesis of 5*H*-[1,3]thiazolo[2,3-b]quinazolin-5-ones **38** and 12*H*-[1,3]benzothiazolo[2,3-b]quinazolin-12-ones **39** from 2-chlorobenzoic acids. Under ultrasonic irradiation, 2-chlorobenzoic acid derivatives **33** underwent copper-catalyzed coupling reaction with 2-aminothiazoles **34** or 2-aminobenzothiazoles **35** to form *N*-aryl AA intermediates **36**&**37** that upon cyclization affording the desired compounds (**Figure 9**) [23].

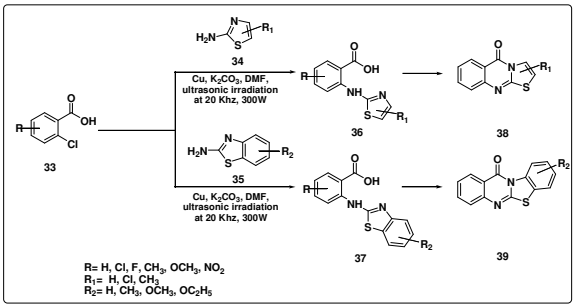

Figure 9: Ultrasonic irradiation synthesis of thiazoloquinazoline and benzothiazoloquinazoline derivatives reported by Docampo *et al*.

In 2012, another methodology for the construction of *N*-aryl AAs via ultrasound-assisted Ullmann reaction was disclosed by Ruby *et al*. The AA derivatives **42** were produced in high yields, under mild reaction conditions and short reaction time (**Figure 10**) [24].

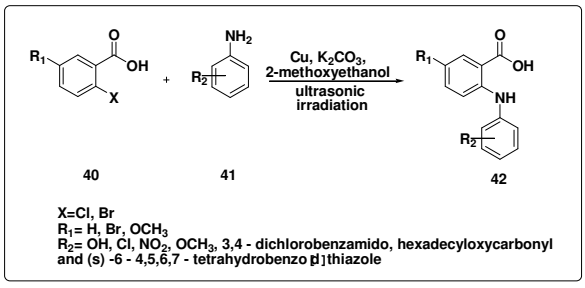

Figure 10: Synthesis of AA derivatives reported by Ruby *et al*.

2.2.1.1.2. Microwave irradiation.

In 2008, Corrêa and co-workers reported using microwave irradiation as a heating source to accomplish the Ullmann coupling reaction between AA derivatives **43** and aryl bromides **44** using copper (I) iodide CuI as a catalyst, L-proline as a ligand and potassium carbonate, K_2CO_3 as a base affording *N*-aryl AAs **45** in good yields (**Figure 11**) [25].

Later, Sarrafi *et al* reported a microwave-assisted chemoselective copper-catalyzed approach for the synthesis of *N*-aryl AAs **48.** Under microwave irradiation, 2-chloro and 2-bromobenzoic **46** was reacted with aromatic amines **47** under solvent free conditions in presence of K_2CO_3 as a base and copper

acetate as a catalyst. This methodology has many advantages like high chemoselectivity, relief work up procedures, short reaction times and no acid protection (**Figure 12**) [26].

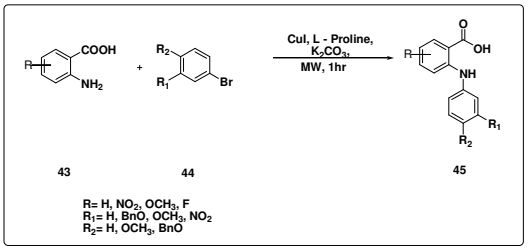

Figure 11: Synthesis of *N*-AAs through Microwave-assisted Ullmann reaction

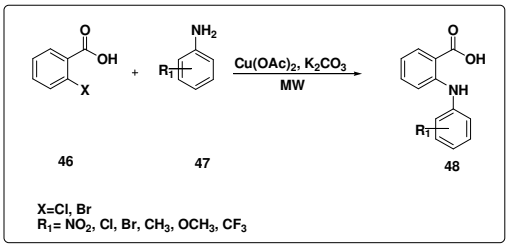

Figure 12: Synthesis of *N*-aryl AA derivatives disclosed by Sarrafi *et al*.

2.2.2. Palladium-catalyzed coupling reaction.

Buchwald–Hartwig amination reaction was firstly reported 1995, in which aryl chlorides react with aliphatic or aromatic amines through palladium-catalyzed C-N cross-coupling reaction [27,28]. This method was used for the construction of many *N*-alkyl and *N*-aryl AA derivatives. Csuk and co-authors reported a convenient and high yield methodology for the synthesis of methyl anthranilates **51**, in which methyl 2-iodobenzoates **49** were reacted with different anilines **50** in presence of Palladium(II) acetate, $Pd(OAc)_2$ as a catalyst, Bis[(2-diphenylphosphino)phenyl] ether, DPE-Phos as a ligand and cesium carbonate, Cs_2CO_3 as a base (**Figure 13**) [29].

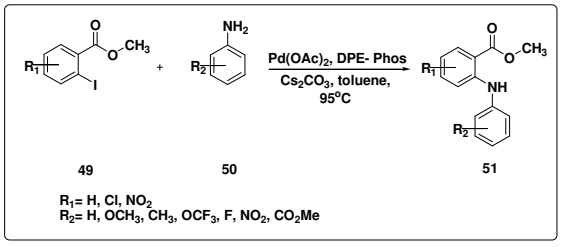

Figure 13: Synthesis of *N*-aryl AAs *via* palladium-catalyzed C-N cross-coupling reaction

2.3. Palladium-catalyzed carbonylation reaction.

1981, LeMahieu and co-workers reported a new route for the production of substituted AA derivatives **54** *via* palladium-phosphine complex catalyzed carbonylation reaction starting from 2-substituted bromoaniline **52** and using Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$ and Bis(triphenylphosphine)palladium(II) dichloride, $Pd(PPh_3)_2(Cl)_2$ as a strong and easy handled catalyst , trienthylamine, n-Bu_3N as a base and carbon monoxide, CO as a carbon source (**Figure 14**) [30].

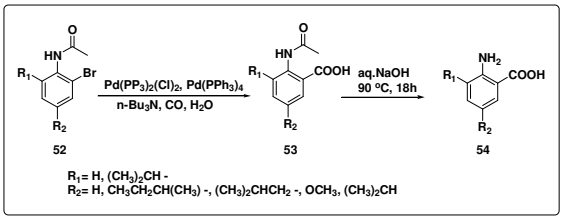

Figure 1: Construction of substituted anthranilics *via* palladium-phosphine complex catalyzed carbonylation reaction

2.4. Metal-catalyzed ortho amination reaction.

2.4.1. Pd-catalyzed ortho-C–H amidation reaction.

Ng and coworkers represented an efficient approach for the synthesis of AA derivatives **57** through Pd-catalyzed ortho-C–H amidation of benzoic acid derivatives. The involved procedures represented the reaction of substituted lithium benzoates **55** with ethyl N-nosyloxycarbamate in dioxane **56** at 90°C for 4-6 hr using potassium acetate, KOAc as a base and palladium (II) acetate, $Pd(OAc)_2$ as a catalyst (**Figure 15**) [31].

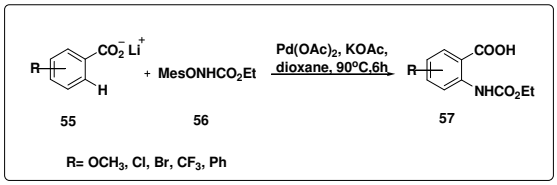

Figure 2: Synthesis of AA derivatives disclosed by Ng and coworkers

2.4.2. Iron-catalyzed ortho amination reaction.

Matsubara *et al.* disclosed a new convenient synthetic methodology for the preparation of AA derivatives. This method is based on iron-Catalyzed ortho amination of aromatic carboxamides with *N*-chloroamines. The starting material, *N*-(quinolin-8-

yl)benzamide **58** was firstly reacted with a mixture of Tris(acetylacetonato) iron(III), Fe(acac)$_3$, 1,2-bis[bis(4-fluorophenyl)phosphino]benzene, F-dppbz and Grignard reagent, PhMgBr yielding iron intermediate **59** (**Figure 16**). Then the reaction was finished just after the addition of *N*-chloromorpholine and afforded the desired AA derivatives **60** in high yields [32].

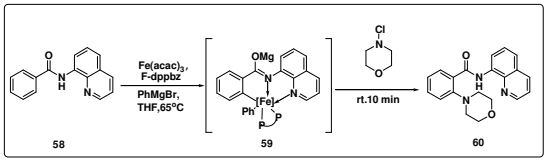

Figure 3: Synthesis of AA analogues reported by Matsubara *et al*.

2.5. Metal free synthetic approaches.

In 2006, Baqi and Müller reported a Catalyst-Free Microwave-Assisted methodology for the synthesis of *N*-substituted 5-nitro anthranilic acid derivatives **63**. The starting material, 5-nitro-2-chlorobenzoic acid **61** was subjected to microwave-assisted, regioselective amination with a multiple range of aromatic and aliphatic amines without addition of any catalyst or solvent. The desired products were afforded in a very high yield (>99%) only within 5-30 min (**Figure 17**) [33].

In 2012, Lan *et al* also used 2-chloro-5-nitrobenzoic acid **61** as a starting material for the construction of the *N*-phenyl AA derivatives **65** through its reaction with a various range of anilines **64** in superheated water and without addition of any catalyst (**Figure 18**) [34].

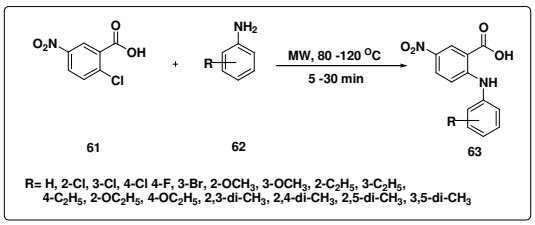

Figure 4: Catalyst-free microwave-assisted construction of *N*-substituted phenyl-5-nitroanthranilic acid derivatives reported by Baqi *et al*.

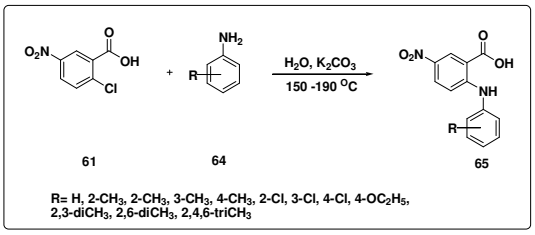

Figure 5: Synthesis of substituted AA derivatives reported by Lan *et al*.

Culf and coworkers demonstrated a new one-pot reaction approach for the construction of AA derivatives **68**. This S_NAr reaction involved the reaction of substituted 2-fluorobenzoic acid **66** with diisopropylcarbodiimide (DIC) **67** in solvent mixture of 1-Propanol (*n*-PrOH) and *N*-Methyl-2-pyrrolidone (NMP) (**Figure 19**). This methodology is simple, metal free, regiospecific and tolerable for 2-florobenzoic acid with many electron withdrawing substituents[35].

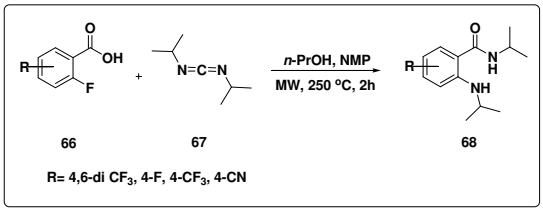

Figure 6: One pot synthesis of AA analogues reported by Culf and coworkers

3. Biological activity of anthranilic acid derivatives.

3.1. Anti-cancer& antimicrobial activity:

Shi *et al* reported the construction of a novel series of anthranilic diamides derivatives having aryl-isoxazoline moiety. *In vitro* anti-cancer potency was evaluated at micromolar, µM level against different types of cancer cell lines like NCI-H460 (human lung cancer cell line), SGC-7901& BGC-823 (gastric cancer cell lines), MCF-7 (breast epithelial adenocarcinoma cell line) and HepG2 (hepatocellular liver carcinoma cell line) using 5-flouro uracil as a reference drug. Compounds **69** and **70** showed a significant inhibition activity against all of the tested cell lines at 40 µg/mL concentration and growth inhibition 59.2-76.3 %. Moreover, compound **71** exhibited a selective inhibition activity against human hepatocellular liver carcinoma cell type

(HepG2) with growth inhibition 50.6±11.5 % (**Figure 20**) [36].

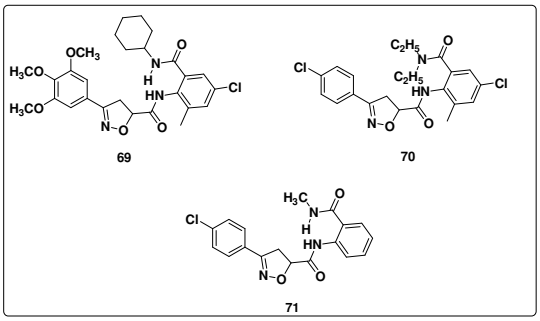

Figure 20: Structures of potential anti-cancer based anthranilic diamides derivatives reported by Shi *et al.*

Onnis and co-workers synthesized a series of (hetero)aryl esters of *N*-(2-(trifluoromethyl)-pyridin-4-yl) AA derivatives based on the flufenamic acid scaffold. The prepared compounds were evaluated for their antiproliferative activity against a list of almost 60 cell lines derived from leukemia, colon, lung, melanoma, CNS, renal, ovarian, prostate, and breast human cancers. Compounds **72** and **73** were the most potent molecules against the majority of the tested cell lines at nanomolar concentrations (**Figure 21**). By using compare analysis, the authors believed that the most potent compounds exhibited their antiproliferative activity via COX-dependent/independent mechanisms [2].

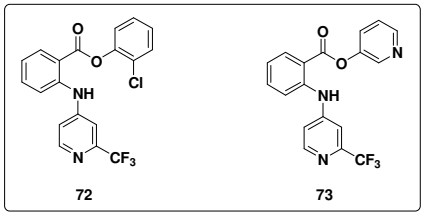

Figure 21: Structures of AA derivatives based on flufenamic acid scaffold with potential anticancer potency

Wang *et al* represented a synthetic approach for the construction of three Cu(II) complexes based on fluorinated AA derivatives [Cu(L^1)(phen)] 74, [Cu(L^2)(phen)] **75** and [Cu(L^3)(phen)].2H_2O **76** (L^1=4-fluoro-2-(picolinamido)benzoic acid, L^2=4,5-difluoro-2-(picolinamido)benzoic acid, L^3=4,5-difluoro-2-((2-hydroxybenzylidene)amino)benzoic acid, phen =1,10-phenanthroline) (**Figure 22**). The authors proved the interaction affinity between the synthesized complexes and calf-thymus DNA *via* using UV absorption, fluorescence spectroscopy and viscosity measurements. Complex **76** achieved the highest DNA binding affinity. Furthermore, they evaluated the anticancer activity of the constructed compounds against A549 (human pulmonary carcinoma cells), Jurkat (human T lymphocyte cell line) and HepG-2 (human liver hepatocellular carcinoma cells) along with testing the antimicrobial activity using the agar-well diffusion method against *E.coli* (Gram-positive) and S.aureus (Gram-negative). The biological data indicated that complex **76** also acquired the highest activity against the three tested cancer cell lines (IC_{50}= 1.42, 1.22, 7.09 µM for A549, HepG-2 and Jurkat, respectively) and bacteria. The authors assumed that the inhibition activity of complex **76** was attributed to two reasons. Firstly, the higher lipophilic character of complex **76** due to two fluoride atoms on the phenyl ring that could enhance its ability to cross the cell membrane. Secondly, complex **76** showed the highest DNA binding affinity, indicating that these complexes might target DNA to promote cell death [37].

In 2019, Fan and co-workers designed and synthesized two cobalt complexes [Co_2(L)(phen)(Ac)(PLC)] **77**, [$Co_3(HL)_4(CH_3O)_2(H_2O)_2$] **78** and one zinc complex [Zn_2(L)(phen)(Ac)(PLC)] **79**, (L = (2-carboxylato-5-(trifluoromethyl)phenyl) (3-hydroxy-4-methoxyphenoxy)amide, phen =1,10-phenanthroline, Ac = acetate, PLC =2-amino-4-trifluoromethylbenzoate) (**Figure 22**). The anticancer activity was evaluated against A549 (human lung cancer cells) and Hela (human cervical cancer cells). Moreover, the antimicrobial potency of the prepared complexes against *E. coli* (Gram-positive) and *S. aureus* (Gram-negative) using the agar-well diffusion method was also scanned. It was found that the zinc complex **79** was the most active molecule with a significant activity towards both A549 (IC_{50} =1.369µM) and Hela (IC_{50}= 2.129µM). Antibacterial results also showed that complex **79** had the highest activity. The authors supposed that the high lipophilic fluorine- containing complex with Zn central atom exhibited better antitumor potency [38].

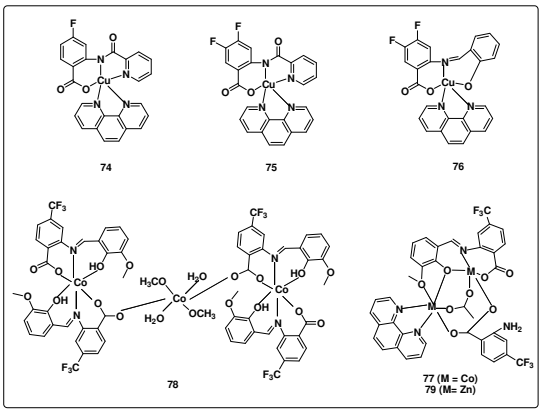

Figure 22: Structures of AA- metal complexes with anticancer activities

The synthesis of series of 4-substituted benzenesulfonamides of AA was reported by Prachayasittikul and co-workers. The synthesized compounds were screened for cytotoxic, antifungal and antibacterial activity. The antiproliferative potency was examined against four cell lines (MOLT-3, HepG2, HuCCA-1 andA549) using etoposide and doxorubicin as reference drugs. The synthesized compounds except compound **81** exhibited cytotoxic activity against MOLT-3 cell line and compound **80** was the most potent one (IC_{50} = 15.71±0.70 µg/mL). In addition, the antibacterial activity was checked against eighteen strains of gram- negative and gram-positive bacteria (**Figure 23**). Unfortunately, none of the synthesized compounds possessed antibacterial activity. Nevertheless, all sulfonamides derivatives showed antifungal activity against *C. albicans* at micro molar concentration (4µg/mL) [39].

In 2013, Shun Li *et al* reported the isolation and characterization of some AA derivatives from *Penicillium paneum* fungus (SD-44) found in deep sea sediment. The anticancer and antimicrobial activity of the isolated compounds were investigated. The cytotoxic activity was screened against two cell lines, Hela (human epithelial carcinoma cell line) and RKO (human colon cancer cell line) using fluorouracil as a reference drug. The biological data revealed that compound **84** and **85** showed a potent anti-proliferative activity against RKO cell line (IC_{50} = 8.4 and 9.7 µM, respectively), while compound **86** exhibited cytotoxic activity against Hela cell line (IC_{50} = 6.6 µM) which in both cases higher than the reference drug, fluorouracil (IC_{50} = 25.0 µM against RKO cell line and 14.5 µM against Hela cell line) (**Figure 23**). Moreover, the antimicrobial activity was performed against two bacteria (*Staphylococcus aureus* and *Escherichia coli*) and three plant-pathogenic fungi (*Alternaria brassicae*, *Fusarium graminearum*, and *Rhizoctonia cerealis*), but unfortunately with no obvious activity [40].

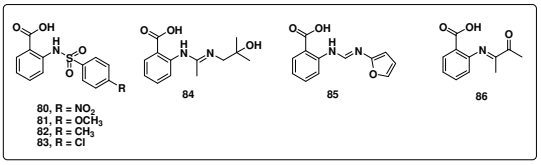

Figure 23: Structures of potential anticancer candidates bearing AA scaffold

In 2013, Liu *et al* synthesized a novel series of anthranilamide derivatives and evaluated their antiproliferative activitiy against two cell lines, HCT- 116 (human colon carcinoma cell line) and MDA-MB-231 (human breast adenocarcinoma cell line). Compounds **87- 92** exhibited a promising inhibition activity against the both cell lines and compound **89** was the most potent one (IC_{50} = 14.6µM and 13.86µM against HTC-116 and MDA-MB-231 respectively) (**Figure 24**). Flow cytometric analysis revealed that compound **89** suppressed the proliferation of both cell lines through induction of apoptosis in a dose-dependent manner and arrest G1 and S phase in the cell cycle [41].

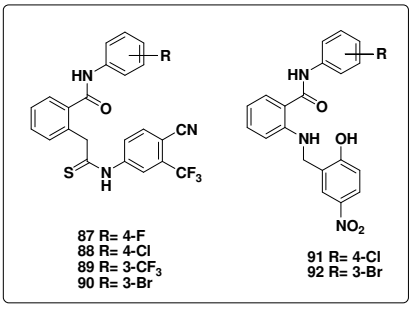

Figure 24: Structures of anthranilamide derivatives with anticancer activity synthesized by Liu *et al*.

El-Shafiey *et al* designed and prepared two AA derivatives, *N*- (2- carboxyphenyl) salicylideneimine, ($H2L^1$) and *N*-(2-carboxyphenyl) thiopheneimine, (HL^2) and used them as a ligand for the synthesis of binary Co (II), Ni (II), Cd (II), Fe (III) and UO_2 (II) metal complexes and ternary pyridine metal complexes. The antibacterial activity of these synthesized ligands, binary and ternary complexes were evaluated against *bacillus subtilis, Escherichia coli* and *bacillus cereus*. The biological data revealed that compounds **93**-**96** were the most active

compounds against the tested bacterial species (**Figure 25**) [42].

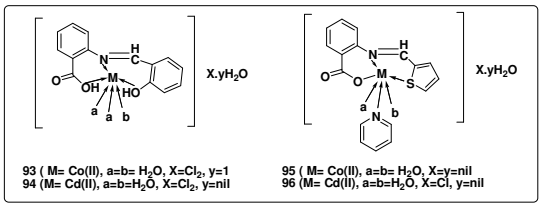

Figure 7: Structures of AA metal complexes with potential antibacterial activity

3.2. Anti-inflammatory activity.

Fenamates including mefenamic acid **97**, tolfenamic acid **98**, flufenamic acid **99**, and meclofenamic acid **100** are considered a very important class of non-steroidal anti- inflammatory drugs NSAID (**Figure 26**). Their anti-inflammatory & analgesic activity are accomplished *via* inhibiting the cyclooxygenase (COX) enzymes which in turn lead to inhibition of the synthesis of prostaglandins. The COX enzymes are found in two isoforms: COX-1, involved in keeping healthy body functions like gastrointestinal tract, platelet, renal and other normal functions and COX-2 that is implicated in the synthesis of prostaglandins which are considered a vital mediators of inflammation, fever and pain [43].

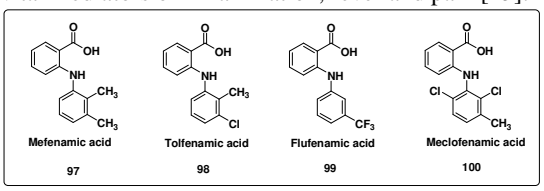

Figure 8: Structures of some marketed available nonsteroidal anti-inflammatory fenamates

Borne *et al* prepared a series of substituted *N*-benzenesulfonyl AA derivatives and investigated their anti-inflammatory activity using erythrocyte membrane stabilization and carrageenin-induced rat paw edema assays. Among the investigated compounds, *N*-*p*-bromobenzenesulfonylanthranilic acid **101** was the most active molecule and gave better results than phenylbutazone, the reference drug in the both two assays (**Figure 27**) [6].

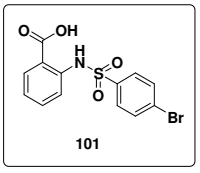

Figure 9: Structure of para-bromo *N*-benzenesulfonyl anthranilic acid with anti-inflammatory activity prepared by Borne *et al.*

The construction of novel sets of AAs was reported by Kumar *et al*. *In vivo* anti-inflammatory activity was tested for all of the constructed compounds using carrageenin-induced rat paw edema assay. The biological data showed that compound **102** and **103** had the highest anti-inflammatory activity (% inhibition of oedema= 50.66% and 47.56% respectively) at dose of 50 mg kg^{-1}, which were better than phenylbutazone, the reference drug (45.52%) (**Figure 28**) [44].

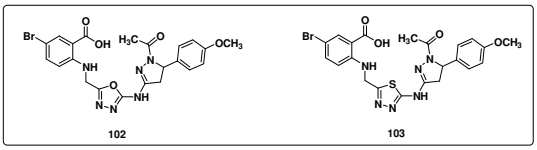

Figure 10: Structures of anti-inflammatory candidates bearing AA scaffold reported by Kumar *et al*.

In 2013, Selley and co-workers studied *in vivo* analgesic& anti-inflammatory activity of *N*-(3′,4′-dimethoxycinnamonyl) anthranilic acid using collagen-induced arthritis assay, a mouse model of rheumatoid arthritis (**Figure 29**). They found that the studied compound **104** decreased the clinical and histological severity of arthritis, reduced the pain and abolish the thermal and mechanical hyperalgesia . It also reduced Th1 cell activity in lymph node cell cultures and elevated serum levels of IL-10. The authors also studied the *in vetro* anti-inflammatory activity of compound **104** and founded that it caused suppression of IFNγ production and proliferation of both B and T lymphocytes [45].

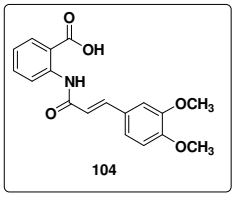

Figure 11: Structure of *N*-(3′,4′-dimethoxycinnamonyl)anthranilic acid with potential anti-inflammatory& analgesic activities

Joshi *et al* prepared a series of *N*-aryl AA derivatives and evaluated their anti-inflammatory activity using carrageenan induced rat paw edema method. The results exhibited that compounds **105** was the most active one with % inhibition 68.54% (**Figure 30**) [46].

Srivastava and co-worker represented the synthesis and testing of analgesic &anti-inflammatory activity of series of 2-(4-oxo-2-phenylthiazolidin-3-yl)-5-(phenylazo)benzoic acids. The anti-inflammatory

activity was performed using paw edema inhibition test and the reference drug was phenylbutazone. The analgesic activity carried out using acetic acid writhing test in presence of reference drug, aspirin. Among the prepared compounds, the most potent compound in comparison with the standard drug at all doses tested was **106** (**Figure 30**) [47].

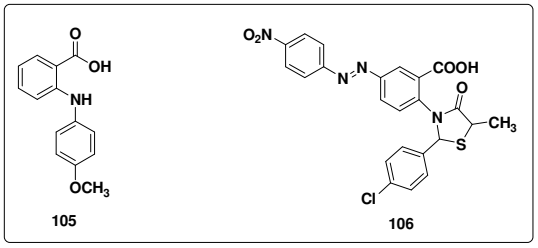

Figure 30: Structures of AA derivatives with analgesic& anti-inflammatory activity

Bala *et al* designed and prepared a novel sets of *N*-phenyl AAs bearing 1,3,4-oxadiazoles scaffold and scanned their anti-inflammatory& analgesic activity in addition to molecular docking studies to survey their binding affinity to cyclooxygenase-2 enzyme. The anti-inflammatory activity was performed using carrageenan-induced rat paw edema assay while the analgesic activity was performed using tail immersion method. The docking study indicated that compound **107** and **108** (**Figure 31**) formed a good interaction with COX-2 enzyme which explained the higher analgesic and anti-inflammatory activity of them. The authors believed that the good docking scores of compounds **107**&**108** was due to exchange of the free carboxylic group, responsible for gastric side effects with heterocyclic 1,3,4-oxadiazole bioactive core [48].

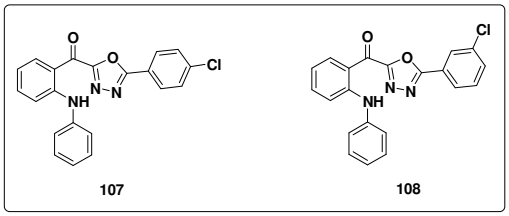

Figure 31: Structures of *N*-phenyl AA derivatives bearing 1,3,4-oxadiazole scaffold with potential analgesic & anti-inflammatory activities produced by Bala *et al*.

3.3. Human Aldo-Keto Reductase inhibition activity.

Human aldo–keto reductases AKR1C1–AKR1C4 are a NAD(P)H linked oxidoreductases superfamily that play a very vital role in the inactivation and biosynthesis of steroid hormones, neurosteroids, xenobiotics, products of lipid peroxidation and prostaglandins [49]. They regulate the activity of androgens, estrogens, progesterone *via* regulating the ligand occupancy and activating their corresponding nuclear receptors. Human hydroxysteroid dehydrogenase AKR1C1 (20αHSD) involved in the reduction of the potent progesterone **109** to the weak 20α-hydroxyprogesterone **110**, which in turn decreases the levels of progesterone in the peripheral tissue. The other important member of aldo–keto reductases superfamily is AKR1C3 (17β- HSD), a peripheral 17 β -hydroxysteroid dehydrogenase. Its main function is the reduction of the weak androgen, androstenedione **111**, to the potent androgen, testosterone **112**, along with the conversion of the weak estrogen, estrone **113** into the potent estrogen, 17β- estradiol **114** using NADPH as a coenzyme **(Figure 32)**. Thus, inhibition of the human AKR1C isozymes becomes an interesting target for the development of many drug regiments used for curing hormone dependent forms of cancer like prostate cancer, breast cancer and endometrial cancer. Recently, various studies indicated that many nonsteroidal anti-inflammatory drugs (NSAIDs) and its derivatives acted as a potent inhibitors of AKR1C isozymes through a non– cyclooxygenase (COX) pathway. In 2003, desmond and co-workers reported the inhibition of AKR1C3 *via* NSAID, indomethacin that prevent the proliferation of human myeloid leukemia cells (HL-60) [50]. Later, Lovering and co-workers represented the crystal structures of AKR1C3 in a complex with NSAIDs, indomethacin and flufenamic acid that provide a structural basis for designing of a new and improved AKRIC isozymes inhibitors with reduced side effects [51].

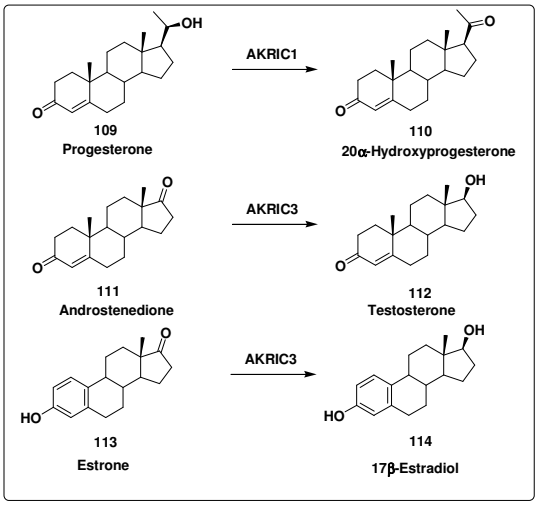

Figure 32: Regulation function of different human AKR1C isozymes

In 2005, Bauman and co-authors reported the synthesis of a series of *N*-phenyl AA derivatives that selectively inhibited recombinant AKR1C isoforms rather than recombinant COX-1 or COX-2 up on testing their inhibition potency against both COX and AKR1C isozymes. The biological data indicated that the IC_{50} values of lead compounds **115 & 116** showed more than 500-fold selectivity for inhibition of AKR1C isozymes in comparison with COX-1 and COX-2 enzymes (**Figure 33**). These results supported the hypothesis that the antineoplastic effects of NSAIDs were mediated by inhibition of AKR1C isozymes rather than cyclooxygenase (COX) isozymes [52].

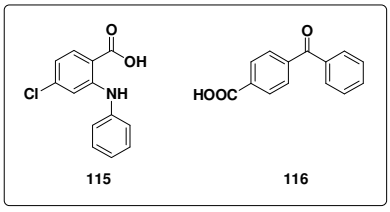

Figure 12: Structures of potential AKR1C inhibitors synthesized by Bauman and co-authors

Gobec *et al* demonstrated the design and construction of a series of compounds based on NSAIDs and evaluated their AKR1C3inhibition activity along with other NSAIDs. Among the prepared compounds, compounds **117**& **118** were the most active inhibitors with IC_{50} 0.68 µM, 11 µM respectively. The authors indicted that NSAIDs, diclofenac sodium **119** and naproxen **120** also showed a good AKR1C3 inhibition activity at low micromolar concentration (IC_{50} = 2.6 µM, 0.48 µM respectively) (**Figure 34**) [53].

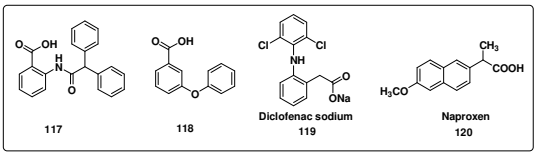

Figure 34: Structures of AKR1C3 inhibitor candidates along with structures of Diclofenac sodium and Naproxen

In 2009, Fishwick and co-workers prepared a sets of pyrimidine, AA and phthalimido derivatives and screened their inhibition activity against AKR1C1.Compound **121** and **122** achieved the highest inhibition activity toward AKR1C1 (k_i = 17µM and 33 µM respectively) (**Figure 35**) [54].

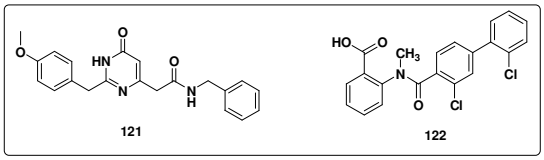

Figure 35: Structures of potential AKR1C inhibitors based on pyrimidine and AA scaffolds prepared by Fishwick and co-workers

Later, Sinreih *et al* prepared a series of *N*-benzoyl AA derivatives and evaluated their inhibition activity against AKR1C isozymes. The results indicated that the prepared compounds acquired an inhibition activity towards AKR1C1–AKR1C3 at micromolar concentration. Furthermore, five selective AKR1C3inhibitors were identified and the most potent compounds were **123** and **124** (IC_{50}= 0.31 µM and 0.35 µM respectively) (**Figure 36**) [55].

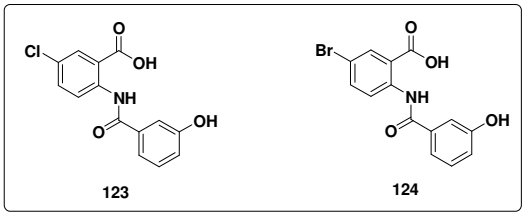

Figure 13: Structures of *N*-benzoyl AA derivatives as AKR1C3 inhibitors synthesized by Sinreih *et al*.

3.4. Anti-HCV activity.

Hepatitis C virus (HCV) is a single stranded RNA virus belonged to the *Flaviviridae* family of enveloped viruses. HCV is the main agent of chronic

hepatitis C infection. It is estimated that 3% of people around the world (170 million) are chronically infected with HCV. The majority of these infections could progress to deadly outcomes like liver cirrhosis, hepatocellular carcinoma and chronic hepatitis[56-58]. HCV NS5B plays a very pivotal role in viral replication process. Its main function is encoding the viral RNA-dependent RNA polymerase (RdRp) activity essential for replicating the viral RNA. Furthermore, it has no functional equivalent in mammalian cells. So, selective inhibition of NS5B has become a promising target for the development of newer anti-HCV drugs [59-61].

Nittoli *et al* designed and prepared a series of AA derivatives and evaluated their inhibition activity towards HCV NS5B polymerase. Compounds **125** & **126** were the most active inhibitors with IC_{50} 17 nM, 10 nM respectively (**Figure 37**). X-ray structure of the enzyme-inhibitor complex indicated that the constructed compounds bind with HCV-NS5B in a region between the palm and thumb regions close to the active site [5].

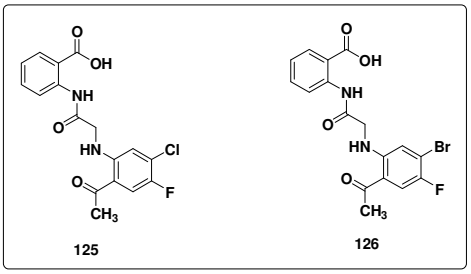

Figure 14: Structures of AA derivatives as HCV NS5B inhibitors prepared by Nittoli *et al.*

In 2013, stammers *et al* demonstrated a fragment based methodology used for the preparation of a novel series of HCV NS5B polymerase inhibitors based on sulfonamide AA scaffold. The analysis of X-ray crystallographic structural complexes of NS5B-inhibitors along with NS5B inhibition enzyme assay results proved that compounds **127** (IC_{50} = 0.22 µM, EC_{50} > 30 µM) and **128** (IC_{50} = 0.16 µM, EC_{50} > 30 µM) achieved the highest anti-viral potency (**Figure 38**) [62].

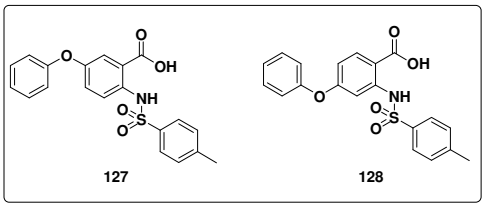

Figure 38: Structures of HCV-NS5B inhibitors based on sulfonamide AA scaffold constructed by stammers *et al.*

Later, Beaulieu and other co-authors optimized the structure of compounds **127** & **128** to improve the cell culture potency. This optimization led to a potent NS5B inhibitor **129** with sub-micromolar inhibition activity (IC_{50} = 0. 0.08 ± 0.04 µM, EC_{50} = 0.095 ± 0.03 µM) (**Figure 39**) [63].

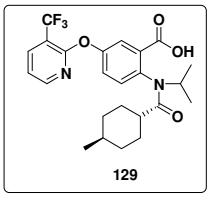

Figure 39: Structure of HCV-NS5B inhibitor based on AA pharmacophore prepared by Beaulieu *et al.*

3.5. Nuclear farnesoid X receptor (FXR) ligand activity.

Nuclear farnesoid X receptor (FXR) is mainly expressed in liver, intestine, and kidney. It is considered a ligand activated transcription factor that plays a pivotal roles in regulation of metabolic pathways like bile acid, cholesterol, glucose homeostasis and other normal body functions. Nowadays, many studies assumed that activation of FXR could be a plausible therapeutic target for the treatment of several pathophysiological conditions like diabetes, primary biliary cirrhosis, nonalcoholic steatohepatitis, and certain forms of cancer[64-66]. In 2014, Merk and co-authors designed and constructed a series of AA derivatives and studied their structure activity relationship (SAR) and *in vitro* activity as a novel FXR ligands. The most active partial FXR agonist was compound **130** (EC_{50} = 1.5 ± 0.2 µM and maximal relative FXR activation = 37 ± 1%). Compound **130** underwent further optimization by Merk and other co-authors affording a very potent partial FXR agonist compound **131** (EC_{50} = 8 ± 3 nM and maximal relative FXR activation =17.5 ± 0.7%) (**Figure 40**) [67,68].

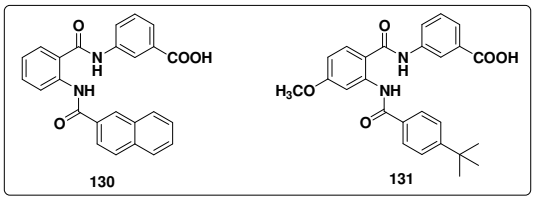

Figure 40: Structures of partial FXR agonists based on AA scaffold

4. Conclusions

AA is a valuable organic scaffold involved in the synthesis and construction of many drugs and drug candidates used in management of numerous types of diseases. Different synthetic approaches of AAs have been discussed. These approaches involved copper-catalyzed Ullmann-Goldberg coupling reaction, palladium –catalyzed coupling reaction, palladium – catalyzed cabonylation reaction, metal-catalyzed ortho amination reaction and metal free synthetic methodologies. Also, the potential therapeutic activity of many newly synthesized or isolated AA derivatives have been demonstrated. AAs showed different biological activities like anticancer, antimicrobial, anti-HCV, analgesic& anti-inflammatory and human aldo-keto reductase inhibition activity.The conclusions section should come in this section at the end of the article, before the acknowledgements.

5. Conflicts of interest

All authors declare that there is no conflict of interest.

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