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Recent Advances in Medicinal Chemistry of Sulfonamides. Rational Design as Anti-Tumoral, Anti-Bacterial and Anti-Inflammatory Agents

Syed Shoaib Ahmad Shah[1], Gildardo Rivera[2*] and Muhammad Ashfaq[1]

[1]*Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur, Pakistan;* [2]*Centro de Biotecnología Genómica, Instituto Politécnico Nacional, 88710, Reynosa, México*

Abstract: Now-a-days, cancer is becoming one of the major problems of public health in the world. Pharmacology treatment is a way to increase quality and long life. Predominantly, in last decade sulfonamide derivatives have been described as potential carbonic anhydrase inhibitors. In the present work, we describe recent advances during the last decade in medicinal chemistry of sulfonamides derivatives with some examples of rational design as anti-tumoral, anti-bacterial and anti-inflammatory agents. We show strategy design, structure-activity relationship, biological activity and advances of new sulfonamide compounds that have more health significance than some clinically used sulfonamides.

Keywords: Anti-bacterial, Anti-inflammatory, Anti-tumoral, Biological activity, Sulfonamide, Structure-activity relationship, Clinical use.

1. INTRODUCTION

The sulfonamide (SO_2–NH-) [1] has great importance in medicinal chemistry, with various biological activities [2-4] such as anti-bacterial [5], hypoglycemic [6], diuretic [7], anti-carbonic anhydrase (CA), anti-thyroid *in vitro* and *in vivo*, anti-inflammatory [8, 9], anti-cancer activities [10], anti-hypertensive [11], anti-convulsant and herbicidal properties for potential agricultural applications [12, 13].

2. ANTI-TUMORAL SULFONAMIDES

Cell proliferation is a consequence of positive signals which promote cell division and negative signals which suppress the process. Key factors in this signaling cascade are a series of cyclin dependent kinases (CDKs) [14]. It has been shown that they are also required for replication of viruses that replicate only in dividing cells, such as adeno- and papilloma viruses as well as in non-dividing cells, such as human immunodeficiency virus 1 (HIV-1) and herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). CDKs are a family of serine/threonine kinases which play a crucial role in cell cycle control and are involved in diverse cellular processes, in regulation of cell division (CDKs 1, 2, 3, 4, 6 and 7), transcription (CDKs 7, 8 and 9) or maintenance of the structure of the cytoskeleton (CDK 5) [15]. CDKs control the cell cycle progression operating at the transition from G2 to M, G1 to S phases, and progression through S phase, regulated by a complex set of mechanisms, including the presence of activating cyclins, regulatory phosphorylations, and endogenous CDK inhibitors at checkpoints [16]. Cell cycle progresses by the activation of cyclin and CDK complexes [17]. These cyclins and CDKs function as check points regulating the transition from one phase of cell cycle to another. Structural studies have explored the active and inactive states of CDK 2. Monomeric form was inactive, while association of cyclin A with CDK 2 and Thr160 phosphorylation results active (CDK 2). CDKs inhibitors decrease the kinase activities of the cyclin/CDK complexes, blocking the transition from G1 to S phases. Activation of CDK 2 results in rotation of N- and C-terminal domains leading to a slight widening of adenosine triphosphate (ATP) cleft [18]. The movement of PSTAIRE helix and Glu51 and the subsequent reorganization leads to reshaping of the phosphate-binding site [19]. In this scope, **AZD5438** (Fig. **1**) showed significant anti-proliferative activity in human tumor cell lines with inhibition constant 50 (IC_{50}) range, 0.2–1.7 μmol/L, causing inhibition of the phosphorylation of CDK substrates pRb, nucleolin, protein phosphatase 1a, and ribonucleic acid (RNA) polymerase II COOH-terminal domain and blocking cell cycling at G2, M, S, and G1 phases [20].

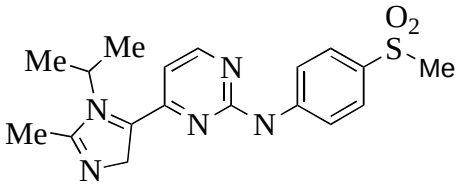

Fig. (1). Structure of compound AZD5438 with anti-proliferative activity in human tumor cell lines.

Structural-activity relationship (SAR) studies showed that the aniline group substitution with sulfonamide was beneficial for CDK 2 activity [21]. Compounds **1a-b** (Fig. **2**) with methyl group substitution on imidazo[1,2-a]pyridine ring display the importance of sulfonamide substitution. A 4-sulfonamide substituted compound **1a** resulted in an increased potency over unsubstituted compound **1b** (IC_{50} = 0.038 μM and IC_{50} = 0.21 μM). Compound **2**, devoid of methyl group substitution on imidazo[1,2-a]pyridine ring

*Address correspondence to this author at the Centro de Biotecnología Genómica, Instituto Politécnico Nacional, Boulevard del Maestro, s/n, Esq. Elías Piña, 88710, Reynosa, México; Tel: +52 899 9243627; Fax: +52 899 9243628; E-mail: gildardors@hotmail.com

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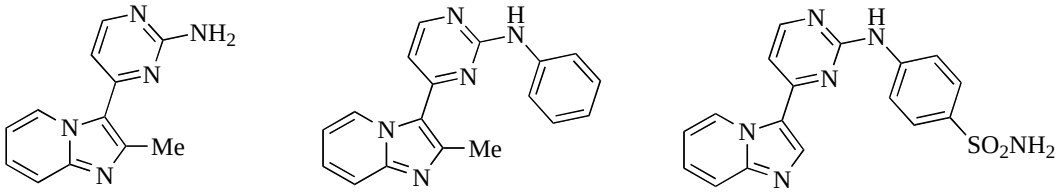
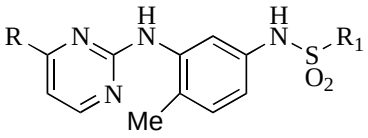


1a **1b** **2**

Fig. (2). Structure of imidazo[1,2-a]pyridine derivatives.

displayed tremendous activity (IC_{50} < 0.003 μM). This was due to the hydrogen bonds formed by *para*-sulfonamide group with backbone NH and carboxylic side chain of Asp86 [22].

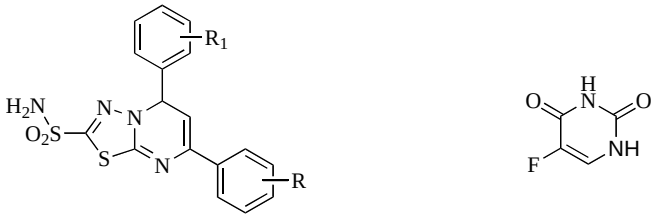
Additionally, we analyzed results of another sulfonamide derivatives as anti-cancer agents, in this scope, compounds **3a-h** (Fig. **3**) were evaluated for their cytotoxicity in selected human cancer cell lines of leukemia (K562) and breast (MCF-7 and MDA-MB-231) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) method. Anilino substituted pyrimidine sulfonamides that exhibit considerable anti-cancer activity. The fluorescence activated cell sorting (FACS) analysis showed more population in sub-G1 phase indicating that these sulfonamides (**3d**, **3e**, and **3g**) possess apoptosis inducing ability. It was observed from the detailed biological studies that there is down regulation of cyclins and CDK 4 indicating cell cycle blocking in the G1 phase in these compounds (**3d**, **3e**, and **3g**), apart from down regulation of NF-kB, protein kinase B (PKB) and signal transducer and activator of transcription (STAT). Based on the above results, compound **3e** could be a potential candidate for undergoing detailed biological investigations for assessing its usefulness in the treatment of cancer [23].



3a R= 3-Pyridyl; R1= 4-Chlorophenyl
3b R= 3-Pyridyl; R1= 4-Biphenyl
3c R= 3-Pyridyl; R1= 2-Naphthyl
3d R= 3-Pyridyl; R1= 3-Quinolinyl
3e R= 3,4,5-Trimethoxyphenyl; R1= 4-Biphenyl
3f R= 3,4,5-Trimethoxyphenyl; R1= 4-Methoxyphenyl
3g R= 3,4,5-Trimethoxyphenyl; R1= 3,4-Dimethoxiphenyl
3h R= 3,4,5-Trimethoxyphenyl; R1= 2-Naphthyl

Fig. (3). Anti-cancer compounds of 4-methyl-3-(pyrimidin-2-ylamino)benzenesulfonamides.

An anti-tumor activity of compounds **4c**, **4f**, and **4j** (Fig. **4**) against Ehrlich Ascites Carcinoma (EAC) in Swiss albino mice the 5th day after inoculation of EAC in mice, increase in body weight and ascites was observed clearly, also the mice became slow and inactive. Mice which received **4j** and 5- fluorouracil were more protected against ascites and showed slight increase in body weight unlike the control group. Mice which received **4c** showed slight toxic symptoms such as dizziness, erection of tail, and became slow. Preliminary biological studies revealed that compounds **4c**, **4f**, and **4j** exhibited the highest affinity to deoxyribonucleic acid (DNA) and showed the highest percentage increase in lifespan of mice inoculated with EAC cells over 5-fluorouracil (positive control) [24].



4a-I **5-Fluorouracil**

4a R= H; R1= H
4b R= H; R1= 4-Br
4c R= H; R1= 4-Cl
4d R= H; R1= 4-NO_2
4e R= H; R1= 4-OCH_3
4f R= H; R1= 3,4-Di-OCH_3
4g R= H; R1= 2,6-Di-Cl
4h R= H; R1= 2-Cl-5-NO_2
4i R= NH_2; R1= H
4j R= NH_2; R1= 4-Cl
4k R= NH_2; R1= 4-OCH_3
4l R= CH_3; R1= H

Fig. (4). 7*H*-[1,3,4]thidiazolo[3,2-α]pyrimidine-2-sulfonamides derivatives (4a-l) and reference drug 5-fluorouracil.

On the other hand, CA are metalloenzymes which catalyze the hydration reaction of carbon dioxide into bicarbonate ($H_2O + CO_2 \leftrightarrow HCO_3^- + H^+$) and are therefore involved in various physiological functions such as pH regulation, respiration, bone resorption, etc [25, 26]. The active site of α-CAs comprises a catalytic Zn^{II} ion coordinated by three imidazole groups of histidines and by one hydroxide ion (or water molecule), all in a distorted tetrahedral geometry. This grouping is located at the base of a cone-shaped amphiphilic depression, one wall of which is

dominated by hydrophobic residues and the other of which is dominated by hydrophilic residues [27]. Two tumor-associated membrane CA isozymes (IX and XII) have been identified, cloned, and sequenced [28-30]. There are a variety of mechanisms for anti-cancer activity of sulfonamides, and the most prominent mechanism is the inhibition of CA isozymes as given in (Fig. **5**) [31].

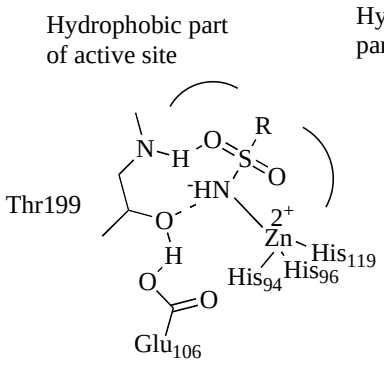
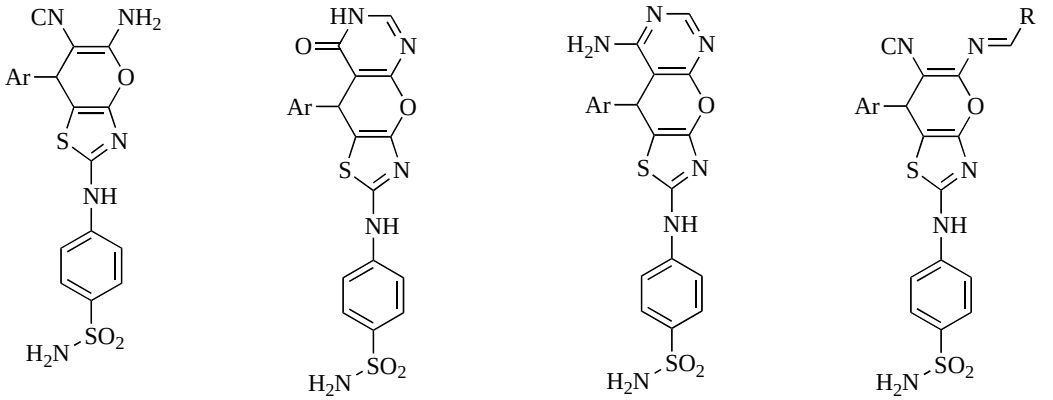


Fig. (5). Inhibition mechanisms of carbonic anhydrase by sulfonamides.

In this scope, there is the synthesis of some new thiazolo[4,5-b]pyrane, thiazolo[4,5-b]pyrano[2,3-d]pyrimidine derivatives bearing a sulfonamide moiety (Fig. **6**). The design of the structures of these compounds complies with the general pharmacophoric requirements for CA inhibiting anti-cancer drugs. The newly synthesized compounds were evaluated for their *in vitro* anti-cancer activity against human breast cancer cell line (MCF7). Most of the screened compounds showed interesting cytotoxic activities compared to doxorubicin as a reference drug. Compounds **5a**, **5b**, **5c**, and **5d** (IC_{50} values of 39.4, 41.6, 35.72, and 34.64 μM, respectively) exhibited higher cytotoxic activities than the reference drug doxorubicin (IC_{50} = 71.8 μM). Additionally, the previously mentioned compounds were evaluated for their ability to enhance the cell killing effect of gamma radiation [32].

The importance of the bridge linking the two phenyl moieties of substituted phenyl 4-(2-oxoimidazolidin-1-yl)benzenesulfonates (PIB-SOs) was assessed using a sulfonamide group, which is a bioisostere of sulfonate and ethenyl groups. Forty one derivatives of phenyl 4-(2-oxoimidazolidin-1-yl)benzenesulfonamide (PIB-SA) were reported with biological evaluation. PIB-SAs exhibit anti-proliferative activities at the nanomolar level against sixteen cancer cell lines block the cell cycle progression in G2/M phase, leading to cytoskeleton disruption and anoikis. These results were subjected to comparative molecular field analyses (CoMFA) and comparative molecular similarity indices analyses (CoMSIA) to establish quantitative SAR.



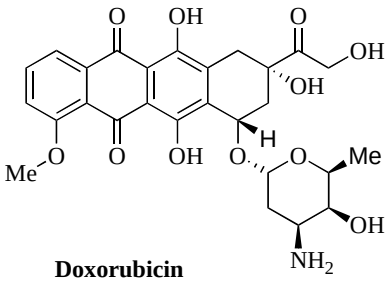
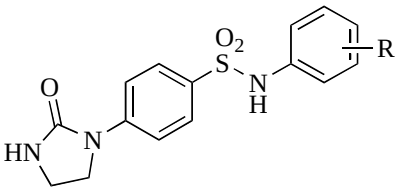


Fig. (6). Structure of 4-(7*H*-pyrano[3,2-*d*][1,3]thiazol-2-ylamino)benzensulfonamides derivatives with cytotoxic activity and reference drug doxorubicin.

These results provide evidence that the sulfonate and sulfonamide moieties are reciprocal bioisosteres and that phenyl-imidazolidin-2-one could mimic the trimethoxyphenyl moiety found in the structure of numerous potent anti-microtubule agents (Fig. **7**). Finally, compounds **6a** and **6b** exhibited potent anti-tumor and anti-angiogenic activities on HT-1080 fibrosarcoma cells grafted onto chick chorioallantoic membrane similar to CA-4 without significant toxicity for the chick embryos, making this class of compounds a promising class of anti-cancer agents [33].



6a R= 3-CH_2CH_3
6b R= 3-OCH_3

Fig. (7). Structure of 4-(2-oxoimidazolidin-1-yl)-*N*-phenylbenzenesulfonamides derivatives.

Sulfonamides possessing CA (EC 4.2.1.1) inhibitory properties such as acetazolamide (**AAZ**), methazolamide (**MZA**), ethoxzolamide (**EZA**), dichlorophenamide (**DCP**) and indisulam (**IND**) (Fig. **8**) have been used for more than 40 years as systemic drugs in the treatment of diseases associated with acid/base secretory disequilibria [34-36]. The main drawback of such agents is constituted by side effects such as augmented diuresis, fatigue, paresthesias, anorexia, etc. due to CA inhibition in other tissues/organs than the target one (CA, in the form of 14 isozymes, is ubiquitous in vertebrates). An anilino substituted pyrimidine moiety present in the structures of agents like **STI571** (Fig. **8**) (imatinib mesylate, gleevec) is considered responsible for the potent antitumor properties [37, 38]. Several sulfonamide compounds bearing an aromatic or a heteroaromatic ring were found to possess potent CA inhibitory activity and so can be used in the treatment of several types of cancer.

Some quinoline and pyrimidoquinoline derivatives (Fig. **9**) containing a free sulfonamide moiety have been shown to exhibit significant anti-cancer activity such as the quinoline derivatives having butanamide **7a**, and benzamide **7b**; the pyrimidoquinoline derivatives having *p*-tolyl **8a** and 4-bromophenyl **8b**. Docking of the compounds in the CA active site may give a suggestion that these compounds may act as CA inhibitors and this may contribute in part to their anti-cancer activity [39].

It was clearly observed that quinolines with either 4-chlorobenzenesulfonamide **21a** or 4-bromobenzene sulfonamide moiety **21b** (Fig. **10**) exhibited higher anti-tumor activity than the reference drug doxorubicin. Also, pyrimidoquinoline derivatives **19a**, **19b**, **20a** and **20b** revealed higher potency than the doxorubicin. In the meantime compound **18** is nearly as active as doxorubicin [40].

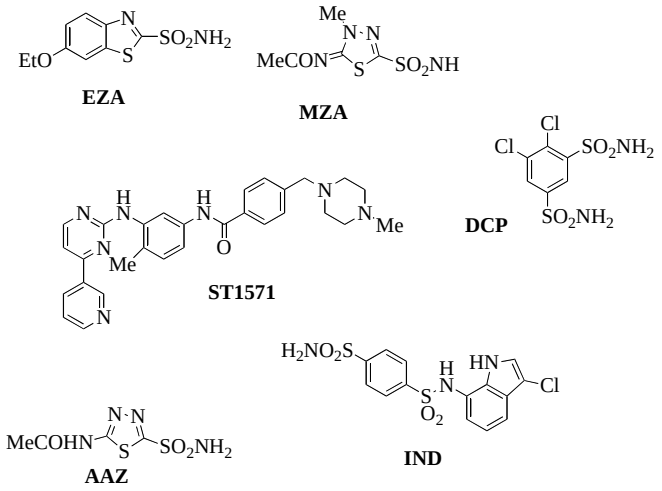
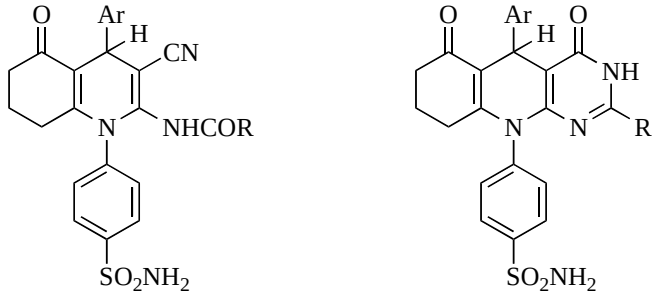


Fig. (8). Structures of sulfa drugs.



7 **8**

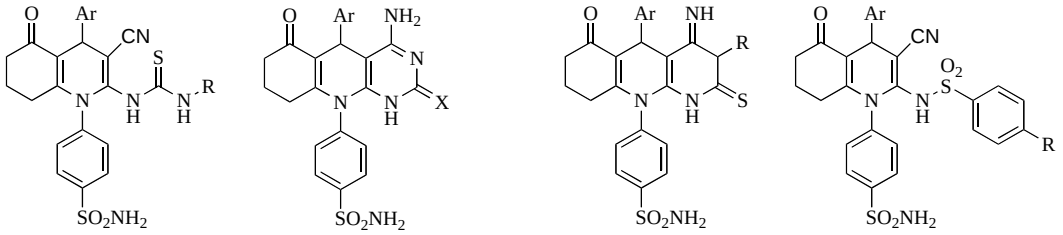
a R= CH_2CH_2Cl
b R= C_6H_5

a R= 4-$CH_3C_6H_4$
b R= 4-BrC_6H_4

Fig. (9). Structure of quinoline and pyrimidoquinoline derivatives with sulfonamide moiety as CA inhibitors.

Pyridine derivatives with sulfonamides moiety showed high to weak inhibitory properties against the slow cytosolic isoform hCA I. The compounds **9c**, **9d** and **11** (Fig. **11**) were slightly more effective inhibitors against hCA I, with K_is in the range of 2.46-4.56 μM. However, the compound **12** acted as a strong hCA I inhibitor (K_i = 0.089 μM), with a comparable potency as the references compounds (i.e., **EZA** or **IND**); **9a-d**, **10a-d**, **11** and **12** showed excellent hCA IX inhibitory efficacy, with inhibition constants of 5.2-18.3 nM, being much more effective as compared to the clinical used **AAZ**, **MZA**, **EZA**, **DCP** and **IND** (K_is range of 24-50 nM).

A quite good inhibition profile of the second tumor-associated isoform, that is, hCA XII has also been observed for all sulfonamides of types: **9a-9d** (K_is = 8.2-16.4 nM); **10a-10b** and **10c** (K_is = 6.1-9.1 nM); **11** and **12** (K_is = 7.5-7.8 nM), and **10d** (K_i = 6.0 nM) [41]. Against two human cultured cell lines, which are cervix carcinoma cell line (HELA) and breast carcinoma cell lines (MCF7) in comparison to the known anti-cancer drugs: 5-fluorouracil and doxorubicin, *in vitro* growth inhibitory activities of



18 **19** **20** **21**

R= 4-Cl-C_6H_5

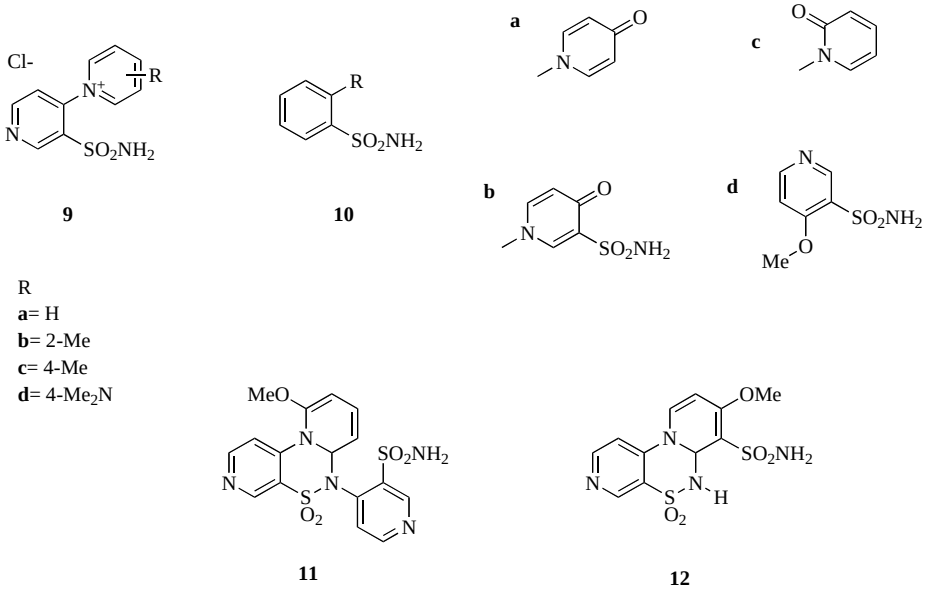
a X= O
b X= S

a R= C_4H_9
b R= 4-Cl-C_6H_5

a R= 4-NO_2
b R= 4-Br

Ar= 2,4-diCl-C_6H_3

Fig. (10). Structure of quinoline sulfonamide derivatives with anti-tumor activity.



9 **10**

R
a= H
b= 2-Me
c= 4-Me
d= 4-Me_2N

11 **12**

Fig. (11). Pyridine derivatives with sulfonamides moiety as CA inhibitors.

compounds **13**, **14**, **15a**, **15b**, **16b**, and **17a** (Fig. **12**) revealed significant potential anti-tumor activity.

Best results were gained by compound **15a** since it showed approximately similar potency against HELA and MCF7 (IC_{50} values of 1.88 and 0.74 mg/mL, respectively) to that of 5-fluorouracil (IC_{50} = 1.01 mg/mL and 0.67 mg/mL, respectively). Also, its benzothiazine analogue **17a** exhibited significant potency against HELA (IC_{50} = 1.48 mg/mL). Considering SAR of the aforementioned selected compounds, they showed narrow range of variation of IC_{50}, being 0.74–3.56 mg/ml. This indicates that SAR of these compounds mainly depends on their main structural feature of: 4-[(pyridin-2-ylamino) sulfonyl] benzene which is considered as the pharmacophoric moiety [42].

The perfluoroalkyl chain is very hydrophobic and it is thought that perfluoroalkanesulfonamides could push back the water which is formed at the time of the enzymatic catalyze. Perfluoroalkanesulfonamides could bind different metal ions in particular divalent cations and the hypothesis is that perfluoroalkanesulfonamides could complex the Zn^{II} metal of the metalloenzyme. It was also shown that $CF_3SO_2NH_2$ could inhibit CA [43, 44]. There is a very sharp difference in inhibition activity on bovine CA (bCA) inhibition, between the perfluoroalkanesulfonamides **22a–e** (Fig. **13**), the sodium salts of perfluoroalkanesulfonamides **23a–c**, the polyfluoroalkanesulfonamides **24a–c** on the one hand and the carbohydrogenated compounds **25a–b** on the other hand. We can deduce that the substitution of hydrogen by fluorine increases the inhibitory activity of these compounds. Thus, perfluoroalkanesulfonamides $CF_3SO_2NH_2$, **22a**, **b**, **d** and the sodium salt of perfluorohexanesulfonamide **23b** showed that IC_{50} are comparable to that of **AAZ** (a clinically used sulfonamide) e.g in the range of 1.380-1.585 μM and 1.351 μM, the sodium salt of perfluoroalkanesulfonamides (**23a–c**) was solubilized in water; they did not need the addition of any cosolvents (DMSO in particular) for the determination of the

inhibition activity on bCA comparatively to other compounds. The perfluoroalkanesulfonamide **22c**, **e** and the polyfluoroalkanesulfonamide **24a**, **b** have shown rather weak inhibitory properties against this enzyme with inhibition constants in the range of 1.901–2.089 μM which is less than that of **AAZ** (1.351 μM). For the polyfluoroalkanesulfonamides (**24**) bCA inhibition varied with the perfluorinated alkyl chain length, C_8F_{17} chain (**24c**) were more inhibitor than those with the C_6F_{13} chain (**24b**), which were also more inhibitor than those with C_4F_9 chain (**24a**). hCA II is generally considered as the main therapeutic target of sulfonamides CA inhibitors. To confirm the study model realized on bCA, it is evaluated the inhibition of hCA II by the compound which present the best inhibition properties (IC_{50}) on bCA in particular the sodium salt of perfluorohexanesulfonamides (**23b**, IC_{50} = 1.380 μM). We found that compound **23b** (IC_{50} = 0.122 μM) was a more potent inhibitor than **AAZ** (IC_{50} = 0.152 μM) on hCA [44].

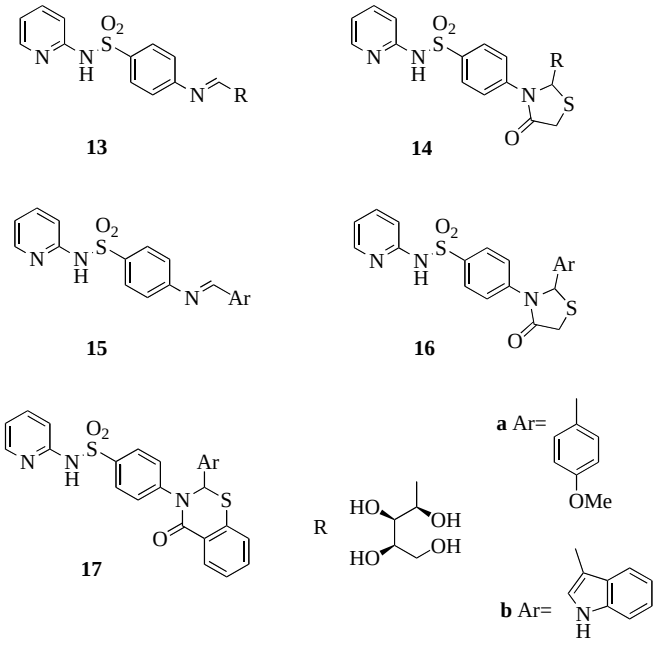
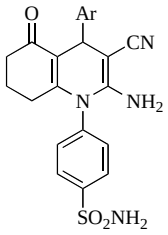


Fig. (12). Sulfonamide derivatives with potential anti-cancer activity.

Doxorubicin is one of the most effective anti-tumor agents used to produce regressions in acute leukemia's Hodgkin's disease, and other lymphomas. The relationship between survival ratio and drug concentration for survival curve of EAC cells, results indicate that substitution with either 4-nitrophenyl **32**, 4-hydroxyphenyl **43**, 2-thienyl **41**, 3-ethoxy-4-methoxyphenyl **35**, trimethoxyphenyl **33** and 2-methoxynaphthyl **37** at 4-position (Fig. **14**) (with IC_{50} values of 2.5, 3, 5, 10, 12, and 12.5 mg/mL, respectively) showed a significant cytotoxic activity which was even higher than that of reference drug doxorubicin with IC_{50} value of 37.5 mg/mL. The substitution in *para* position was found to enhance the cytotoxic activity rather than in *ortho* or *meta* positions. These findings were clearly observed as the presence of 4-nitrophenyl **32** (IC_{50} value of 2.5 mg/mL), and 4-hydroxyphenyl **25** (IC_{50} value of 3 mg/mL) led to an increase in the anti-tumor activity where the percentage of non-viable cells were 85% and 90%, respectively, at a concentration of 10 mg/mL.



26 Ar= CHCH-C_6H_5
27 Ar= 2-CH_3O-C_6H_4
28 Ar= 4-CH_3O-C_6H_4
29 Ar= Piperonyl
30 Ar= Vanillyl
31 Ar= 3-NO_2-C_6H_4
32 Ar= 4-NO_2-C_6H_4
33 Ar= 2,4,5-(CH_3O)-C_6H_2
34 Ar= 2,4-Cl_2-C_6H_3
35 Ar= 4-CH_3O, 3-C_2H_5O-C_6H_3
36 Ar= 2-$OHC_{10}H_6$
37 Ar= 2-$CH_3OC_{10}H_6$
38 Ar= 4-$CH_3OC_{10}H_6$
39 Ar= 2-furyl
40 Ar= 2-furyl, 5-CH_3
41 Ar= 2-thienyl
42 Ar= 4-$CH_3C_6H_4$
43 Ar= 4-OHC_6H_4

Fig. (14). Structure general of quinoline sulfonamides derivatives with anti-tumor activity.

Compound **32** having *para*-nitrophenyl at 4-position is more active than compound **31** bearing *meta*-nitrophenyl at the same position. Also, the presence of methoxy group at *ortho*-position **37** with (IC_{50} value of 12.5 mg/mL) is more active than compound **36** containing hydroxy group at the same position. On the other hand, it was found that compound **41** carrying 2-thienyl at 4-position enhance the cytotoxic activity rather the 2-furyl **39**. In addition, compound having trimethoxy group **33** is more potent than compounds carrying only one methoxy group **27** and **28**. It was very interesting to observe that compound **28** with

22

$R_FSO_2NH_2$

a R_F= C_4F_9
b R_F= C_6F_{13}
c R_F= C_7F_{15}
d R_F= C_8F_{17}
e R_F= $NH_2SO_2(CF_2)_4$

23

R_FSO_2NH-Na+

a R_F= C_4F_9
b R_F= C_6F_{13}
c R_F= C_8F_{17}

24

$R_F(CH_2)_2SO_2NH_2$

a R_F= C_4F_9
b R_F= C_6F_{13}
c R_F= C_8F_{17}

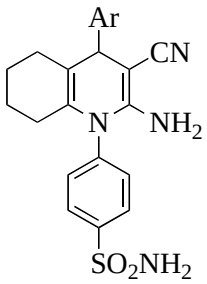
25

$R_HSO_2NH_2$

a R_H= C_4H_9
b R_H= C_8H_{17}

Fig. (13). Perfluorohexanesulfonamides derivatives with potential bCA inhibitory activity.

4-methoxyphenyl at 4-position, compound **30** with 4-hydroxy-3-methoxyphenyl, compound **31** with 3-nitrophenyl and compound **34** with 2,4-dichlorophenyl (IC_{50} values of 25 mg/mL) are nearly as active as **doxorubicin** as positive control, while compounds **42**, **29**, and **38** exhibited a moderate activity but less active than **doxorubicin**. It is clear from the present data that, the comparison of the cytotoxicity of tetrahydroquinoline derivatives against EAC cells has showed that the cell killing potency follows the order **32** > **43** > **41** > **33** > **37** > **doxorubicin**. The presence of a cyano group at 3-position in these compounds is supposed to enhance their anti-tumor activity [45]. It was found that quinoline derivative **44c** carrying benzo[d] [1,3]dioxol at 4-position with (IC_{50} value < 22.2 μM), quinoline derivative **44b** having 4-methoxyphenyl at 4-position with (IC_{50} value of 22.9 μM) and quinoline derivative **44a** having styryl group at 4-position (Fig. **15**) with (IC_{50} value of 23.1 μM) showed higher significant cytotoxic activity which was even higher activity than that of the reference drug **doxorubicin** with (IC_{50} value of 69.9 μM) on EAC cells.

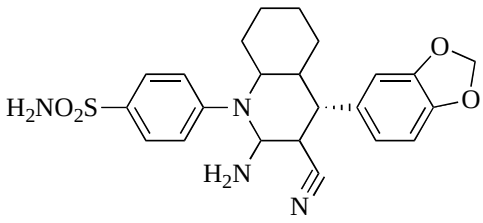


44

a Ar= C_6H_5CH=CH
b Ar= $C_6H_4OCH_3$-4
c Ar= (benzo d,1,3 dioxol-5-yl)
d Ar= C_6H_4OH-4
e Ar= $C_6H_4CH_3$-4

Fig. (15). Quinoline sulfonamide derivatives with cytotoxic activity.

On the other hand, compound **44e** bearing 4-methylphenyl at 4-position with (IC_{50} value of 85.7 μM) and compound **44d** having 4-hydroxyphenyl at 4-position with (IC_{50} value of 82.9 μM) are nearly as active as doxorubicin as positive control. Since, the compounds are sulfonamide derivatives as compound **44c** (Fig. **16**) and their design complies with the general pharmacophore of sulfonamide CA inhibitors, it was interesting to perform docking studies on the synthesized compounds to hCA II and to compare their docking interactions with the previously reported interactions of **IND**. **IND** is a tubulin polymerization inhibitor, which binds reversibly to the colchicine site of β-tubulin [46-49].



44c

Fig. (16). Structure of compound 44c, a sulfonamide derivative.

To give a clearer comparison of the docked pose of **E7070** and the most active compound **44c**. It was found that the benzenesulfonamide moieties bound to hCA II overlap each other completely while the tail adopts a slightly different conformation [50].

In the inhibition study of two cytosolic ubiquitous isozymes of human origin, that is, hCA I and II, and two transmembrane isoforms hCA IX and XII (cancer-associated); the five compound **45c**-**45g** (Fig. **17**) showed hCA I inhibitory activity (K_is = 1.09-1.18 μM) in the same range as the clinically used compounds **MZA** and **DCP**; against the ubiquitous and dominant rapid cytosolic isozymes hCA II, all the compounds acting as weaker inhibitors (K_is in the range of 50.5-172 nM); a quite larger variation of inhibitory activity was observed for the inhibition of the tumor-associated isoform, hCA IX, the remaining derivatives **45a**-**45g**, **46a**, **46b** and **46c** showed excellent hCA IX inhibitory efficacy, with inhibition constants equal 5.2-11.9 nM, being much more effective as compared to the clinically used sulfonamides **AAZ**, **MZA**, **EZA**, **DCP** and **IND**; against the second tumor-associated isoform hCA XII, the compounds **45a**-**45g**, **46a** and **46b** were very effective hCA XII inhibitors (K_is in the range of 8.7-45.2 nM), which are comparable or more effective than those clinically used sulfonamides **EZA** and **DCP**, respectively [51].

In vitro cytotoxic activity was found that the quinoline derivative **48** (IC_{50} = 64.5 μM) is the potent compound, and exhibited a higher cytotoxic activity when compared with the reference drug **doxorubicin** (IC_{50} = 71.8 μM) against MCF7 cell line. Compounds **47**, **49**, and **50** (Fig. **18**) are nearly as active as **doxorubicin**. Consequently, the ability of the two active compounds, **48** and **50**, to enhance the cell killing effect of gamma-irradiation was studied. While when the cells were subjected to the same concentrations of compound **48**, and irradiated with a single dose of gamma-radiation at a dose level of 8 Gy, the IC_{50} value was synergistically decreased to 33.1 μM. Similarly, compound **50** showed IC_{50} value of 71.9 μM when used alone. The IC_{50} value was decreased to 44.4 μM, when the cells were treated with compound **50** in combination with gamma-radiation. We can conclude that using the combination of compound **48** or **50** and ionizing radiation synergistically enhanced growth inhibition on breast cancer cells, compared with each agent alone [52].

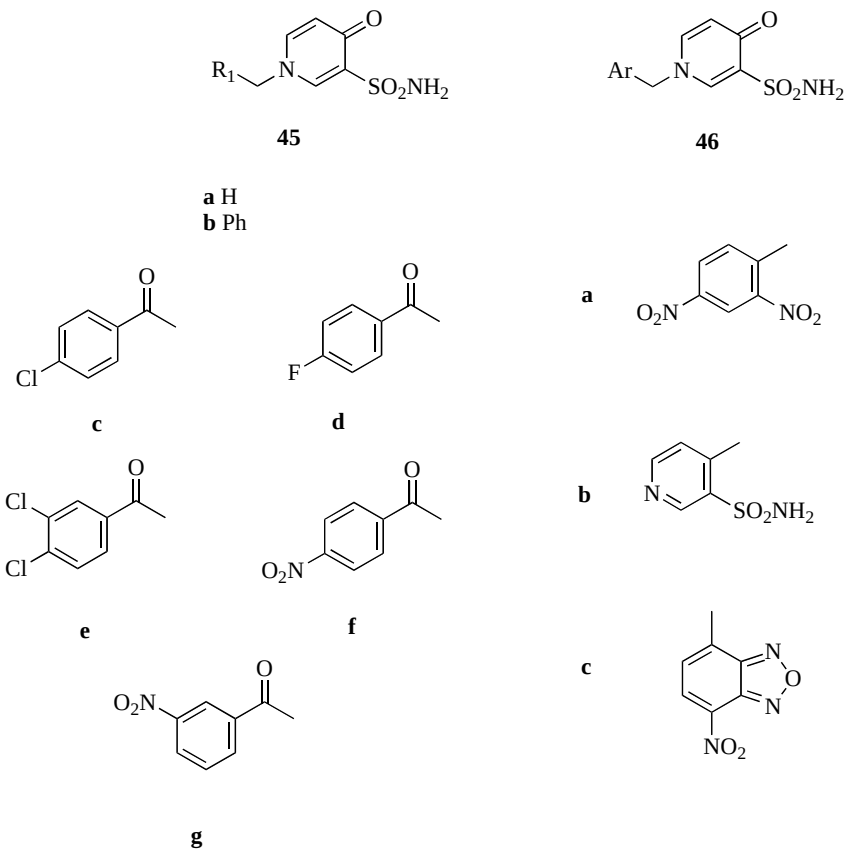


Fig. (17). Structure of 1-substituted 1,4-dihydro-4-oxo-3-pyridinesulfonamides derivatives.

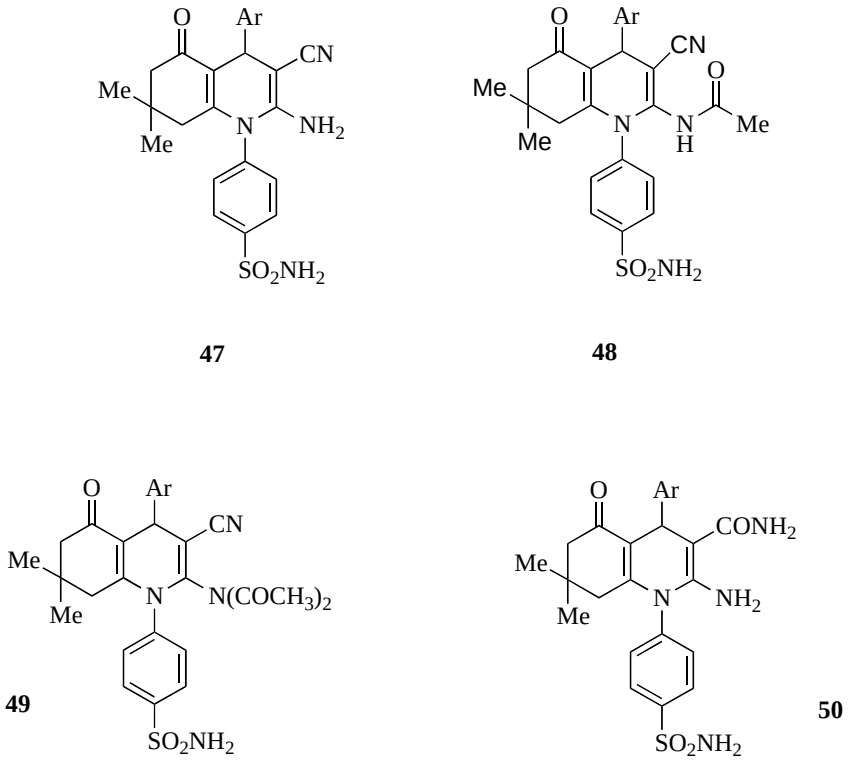


Fig. (18). Quinolines and pyrimido[4,5-b]quinolines bearing a sulfonamide moiety.

Concerning the tetrahydroquinoline derivatives, it was found from the results against MCF7 that the compounds having a substituted sulfonamide with methyl isoxazolyl ring **51b** (IC_{50} = 1.95 μM/mL) and **52b** (IC_{50} = 1.9 μM/mL) were more potent than the unsubstituted ones **51a** ($IC_{50} \geq 10$ μM) and **52a** (IC_{50} = 2.62 μM). Compound **52b** was the most potent in this group. While for the fused tetrahydroquinoline derivatives **53a**–**d** (Fig. **19**), it was found that the unsubstituted sulfonamide derivative **53a** (IC_{50} = 4 μM/mL) was more potent than the substituted ones **53b**–**d** (IC_{50} = 5.17, ≥ 10.9 and 194 μM/mL, respectively). All the compounds show less IC_{50} than doxorubicin (IC_{50} = 0.7 μM/mL) [53].

To evaluate the anti-proliferative effect of **J30** (Fig. **20**) on human cancer cells from several representative solid tumor cell lines: oral carcinoma (KB), nasopharyngeal carcinoma (HONE1), gastric cancer (TSGH and MKN45), kidney cancer (A498), liver cancer (Hep3B), colon cancer (HT29), lung cancer (H460), and glioblastoma multiforme (DBTRG). All cancer cell lines that we tested showed high susceptibility to **J30**, with IC_{50} values ranging between 15 and 20 nM. It is further examined the efficacy of **J30** against drug resistant cell lines. Despite the high level of expression of drug-resistant effluxprotein (MDR/Pgp or MRP) in KB-Vin10, KB-S15, and KB-7D cells, **J30** showed similar cytotoxic efficacy between parental cells and these resistant sublines. **J30** also displayed potent anti-growth activity against a topoisomerase I mutant (HONE1-CPT30) [54].

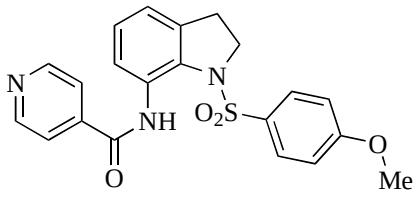


Fig. (20). Chemical structure of compound J30.

The IC_{50} and K_is values, obtained for erythrocytes hCA-I and hCA-II purified by affinity chromatography, were used to compare the inhibitory potential of parent inhibitor **54** (Fig. **21**), **AAZ** and the newly synthesized derivatives on hCA-I and hCA-II. The synthesized compounds (**55a-b**, **56**, **57a-g**, and **58**) (Fig. **21**) have generally more inhibitory effect than **54** (K_i = 5.90 and 7.40 μM) and **AAZ** (6.30 and 3.30 μM) on esterase activity of hCA-I and hCA-II, but the most effective compounds were **57g** (k_i = 0.11 μM) for hCA-I, **55a** (k_i = 0.38 μM), **57f** (k_i = 0.05 μM) and **57g** (k_i = 0.03 μM) for hCA-II [55]. According to the lethal dose 50 (LD_{50}) values of **59** (130.76 mg kg^{-1} in mice, 0.225 mmol kg −1) and chlorambucil (**CBL**) (Fig. **20**) (49.56 mg kg^{-1} in mice, 0.163 mmol kg^{-1}), it can be concluded that the acute toxicity of **59** is lower than that of its mother compound **CBL**. Compound **59** demonstrates high anti-tumor activity and is more potent and safer than its mother compound **CBL**. The concentration of sulfonamides in tumor cells may be related to the basicity of the aromatic amino group and the acidity of

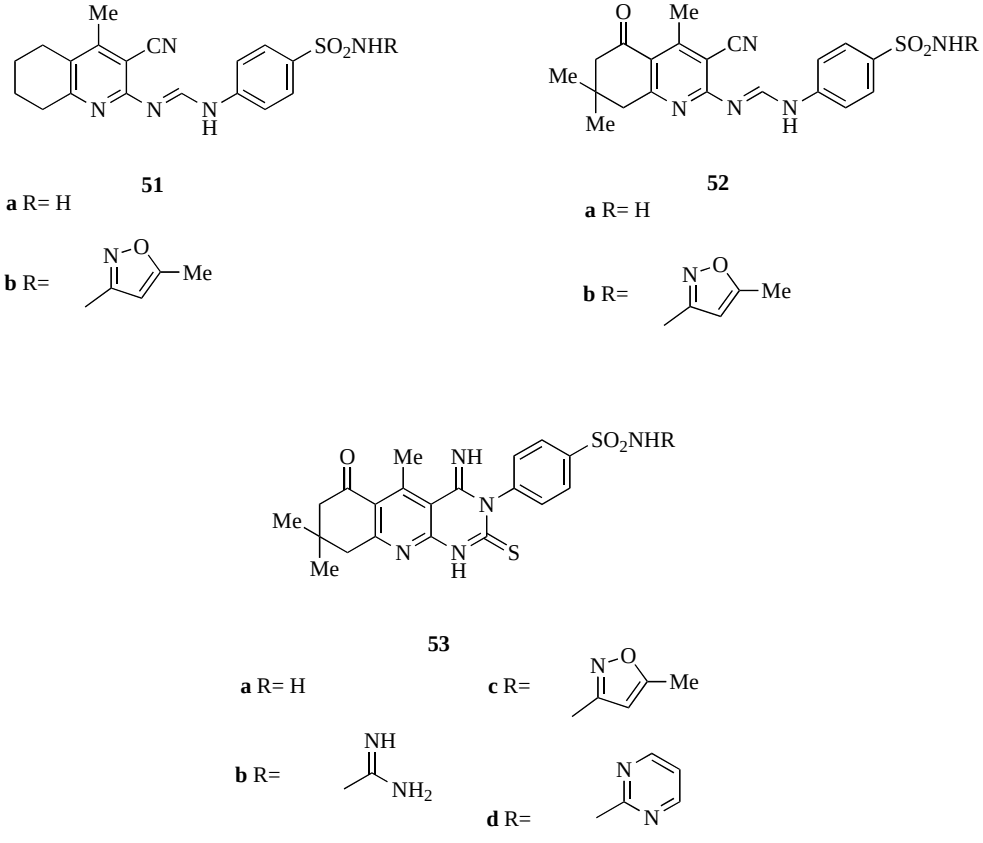


Fig. (19). Quinoline and pyrimido[4,5-b]quinoline derivatives bearing a substituted or unsubstituted sulfonamide moiety.

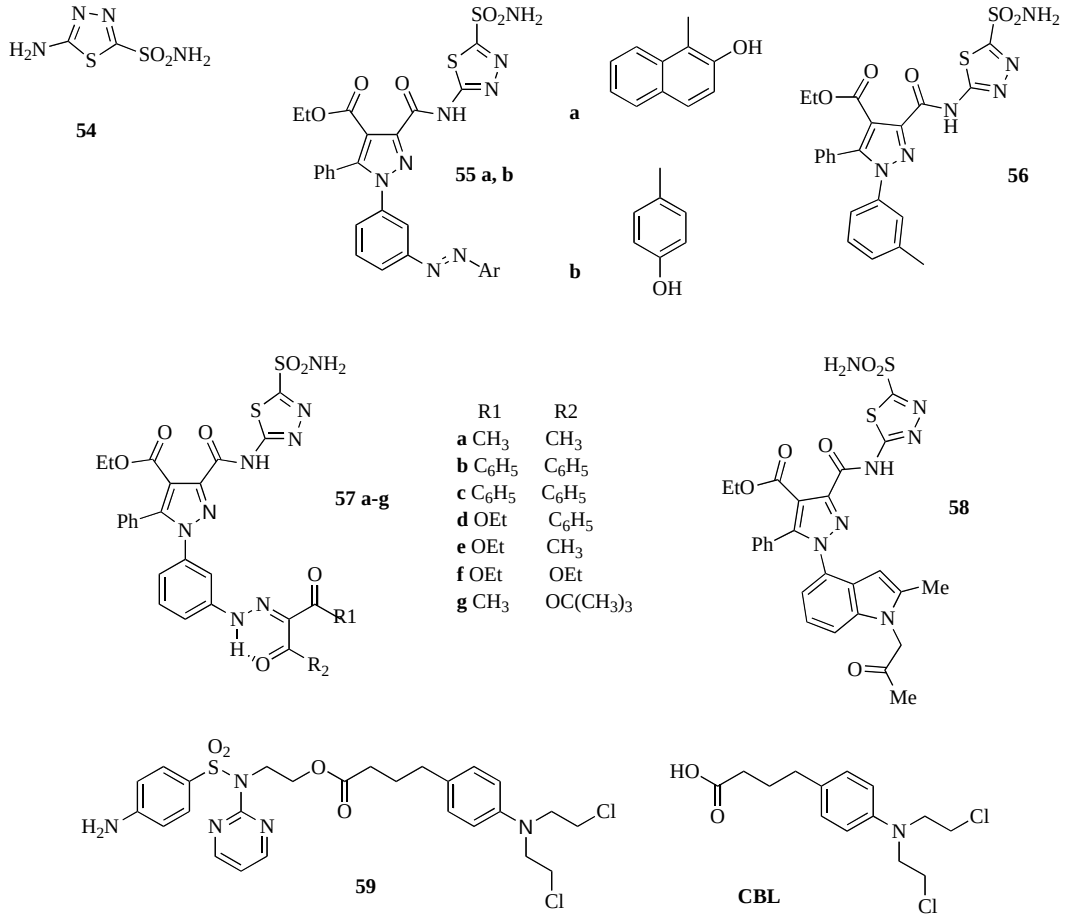


Fig. (21). Sulfonamide derivatives and CBL drugs with anti-tumor activity.

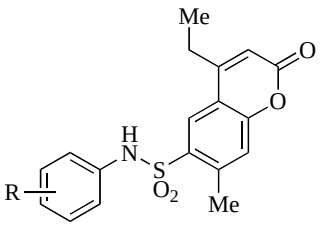
the tumor cells. This class of targeting agents may be further developed to form candidate drugs, which may have advantages over the currently available anti-cancer agents [56].

3. ANTI-BACTERIAL SULFONAMIDES

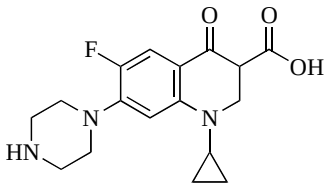
Meanwhile, sulfonamides have attracted increasing attention in the supramolecular chemistry and supramolecular medicinal chemistry [57] since it combined the features required for various biological activities and the metal coordination through phenylamino and sulfonyl amino groups. In particular, Ag-sulfadiazine has been proved to be an effective topical anti-microbial agent, and to be of significance in burn therapy, better than the free ligand or $AgNO_3$. For instance, sulfamethoxazole in combination with trimethoprim is a very active pharmaceutical compound and has been extensively used in clinic as the first choice in the treatment of pneumonia and urinary tract bacterial infections, toxoplasmosis and pneumocystosis in HIV infected patients [58, 59].

Recently, some compounds (Fig. **22**) were evaluated for their *in vitro* anti-bacterial activity against Gram-positive bacteria: *Streptococcus faecalis* (MTCC 3382), *Staphylococcus aureus* (MTCC 3160), *Bacillus subtilis* (MTCC 297); and Gram-negative bacteria: *Pseudomonas aeruginosa* (MTCC 1034), *Klebsiella pneumoniae* (MTCC 3384) and *Escherichia coli* (MTCC 1089) by broth microdilution method. The anti-bacterial data revealed that all the sulfonamides exhibited moderate activity a few of them highly active, but majority of them inactive against *E. coli*. SAR show that compounds with methoxy group **60g**, **60h**, **60i**, **60j** and **60k** were highly active against *S. faecalis* with minimum inhibitory concentration (MIC) of 1 mg/mL. The *meta*-methoxy compound **60h** was found to equally effective against *P. aeruginosa* and *K. pneumoniae* with MIC of 1 and 2 mg/mL, respectively. The 2-chloro compound **60n** and 4-bromo compound **60s** were found to be very active against *S. faecalis*, *P. aeruginosa* and *K. pneumoniae*. Many compounds exhibited MIC similar to **ciprofloxacin** (Fig. **22**) against three bacterial species except *E. coli*. Highest activity was associated with mono-nitro, chloro, bromo and methoxy substituents [60].

The synthesized sulfanilamide derivatives exhibited moderate antimicrobial activities *in vitro*. Especially, compounds **61e**, **62g** and **62i** (Fig. **23**) bearing dodecyl, showed the most potent anti-bacterial activities as compared to chloramphenicol and fluconazole as the reference drugs, against *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *E. typhosa*, *P. aeruginosa*, *S. dysenteriae*, *B. subtilis*, *E. coli*, as well as *C. albicans* and *C. mycoderma* using the two-fold serial dilution technique, having MIC values ranging from 32 to 128 mg/mL. The lengths of the alkyl chain and



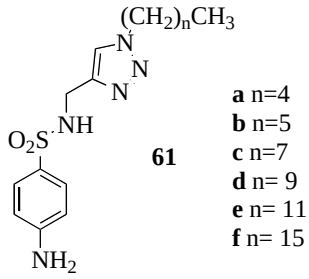
60



Ciprofloxacin

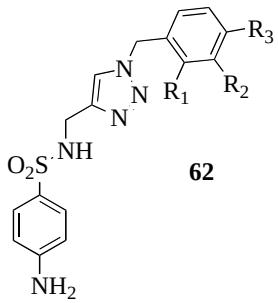
a= H
b= 3-CH_3
c= 4-CH_3
d= 3,4-CH_3
e= 2,4-CH_3
f= 2,6-CH_3
g= 2-OCH_3
h= 3-OCH_3
i= 4-OCH_3
j= 4-OC_2H_5
k= 2-NO_2
l= 3-NO_2
m= 4-NO_2
n= 2-Cl
o= 3-Cl
p= 4-Cl
q= 2,4,-Cl
r= 3,4-Cl
s= 4-Br
t= 3-Cl, 4-CH_3
u= 2-Cl, 5-NO_2
v= 2-NO_2, 4-Cl
w= 2-NO_2, 4-CH_3
x= 2-CH_3, 4-NO_2
y= Naphthylamine

Fig. (22). Structure of oxo-chromene-6-sulfonamides derivatives and ciprofloxacin with anti-bacterial activity.



61

a n=4
b n=5
c n=7
d n= 9
e n= 11
f n= 15



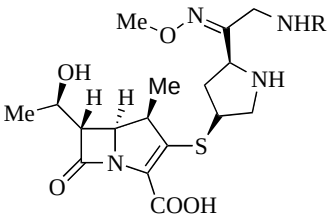
62

a R1= H, R2 = H, R3 =H
b R1= H, R2 = CH3, R3 =H
c R1 = H, R2 = H, R3 = NO_2
d R1 = Cl, R2 =H, R3 = H
e R1 = H, R2 = Cl, R3 = H
f R1 = H, R2 = H, R3 = Cl
g R1 = Cl, R2 = H, R3 = Cl
h R1 = H, R2 = H, R3 = F
i R1 =F, R2 = H, R3 =F

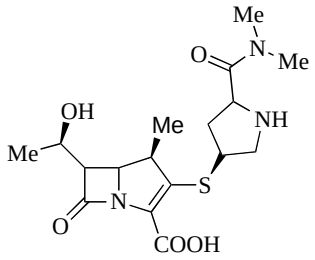
Fig. (23). Sulfanilamide-derived 1,2,3-triazoles.

substitution in the benzyl moiety played important roles in the anti-microbial activities of the title compounds. More importantly, the incorporation of 1,2,3-triazole is helpful to improve the inhibition activity of the sulfonamide precursor *in vitro*. These findings demonstrated that sulfanilamide-derived 1,2,3-triazoles are of biological significance, which have the perspective to become a new member of anti-microbial agents [61].

The *in vitro* anti-bacterial activities of the new carbapenems (Fig. **24**) against both Gram-positive and Gram-negative bacteria with comparison, the MIC values of **imipenem** and **meropenem**. All the compounds displayed superior or similar anti-bacterial activities against Gram-positive tomeropenem, and against Gram-negative bacteria except *P. aeruginosa* to **imipenem**. Alkylaminosulfonamide moieties were generally more potent than the alkylsulfonamide compounds **63a-b**. In alkylaminosulfonamide, as to the substituents on the pyrrolidine chain, the compounds **63c-f**, it also shows that the larger the size of the alkyl substituents, the lower the activity against Gram-positive and Gram-negative bacteria. As expected, methylaminosulfonamide compound **63c** with small alkyl group exhibited the most potent and well balanced activity. Also we observed that acetyl amide substituted compound **63g** is more potent than aminocarbamoyl **63i** against all bacteria. Comparative *in vitro* activities of **63c**, **meropenem**, and **imipenem** against 40 bacterial strains. The selected carbapenem **63c** and possessed excellent *in vitro* activity against target pathogens except *P. aeruginosa*, and superior or similar anti-bacterial activities against Gram-positive to **meropenem**, and against Gram-negative bacteria to **imipenem**. Against *K. pneumoniae*, *E. coil* and *E. cloacae* 63c was 2-4 times more active than the compared **meropenem** and **imipenem** [62].



63



Meropenem

R: **a**= SO_2CH_3, **b**= $SO_2C_2H_5$, **c**= SO_2NHCH_3, **d**= $SO_2NHC_2H_5$
e= $SO_2N(CH_3)_2$, **f**= $SO_2NHC_3H_7$, **g**= $COCH_3$, **h**= H, **i**= $CONH_2$

Fig. (24). 1b-methyl-2-[5-(1-methoxyimino-2-substituted sulfonamide ethyl)pyrrolidin-3-ylthio]carbapenems.

As to the substituent on the pyrrolidine chain, compounds **64h-i** (Fig. **25**) having thiadiazinane moieties were generally more potent than the thiadiazolidine compounds **64a-b** and **64e**. The introduction of alkyl group at N-position of thiadiazolidine (**64a** and **64b**) led to significantly enhanced anti-bacterial activity compared to compounds (**64c-d**) with alkyl substitute at C-3 position. As expected, the existence of N-benzyl group (**64f**) significantly lowered the antibacterial activity compared to compounds (**64a-b**) with methyl and ethyl groups. Comparative *in vitro* activities of **64i**, **meropenem**, and **imipenem** against 40 bacterial strains. The selected carbapenem **64i** possessed excellent *in vitro* activity against target pathogens except *P. aeruginosa*, and superior or similar anti-bacterial activities against Gram-positive bacteria to meropenem, and against Gram-negative bacteria to **imipenem**. Against *E. coli* and *C. diphtheriae*, **64i** was 2-3 times more active than the compared **meropenem** and **imipenem** [63].

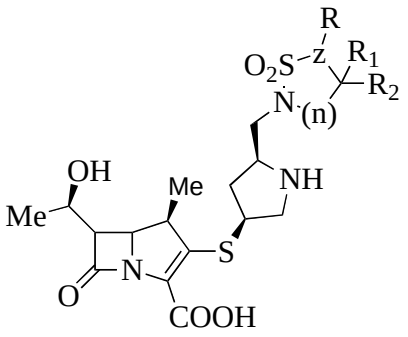
Macrolide antibiotic azithromycin, the first representative of the azalide class, is well-established anti-microbial agent that has been widely prescribed for the treatment of respiratory tract infections owing to its high efficacy and safety [64, 65]. Compounds **65a** and **65b** possess two to three times better activity against inducible methylases (iMLS) resistant *S. pyogenes* strain (MIC, 2 mg/ml) when compared to azithromycin. The introduction of 4-aryl- and 4-heteroaryl-aminosulfonyl groups in **65b-65d** does not improve the activity against iMLS resistant *S. pyogenes* in comparison with **65a**. Compounds **65a-65d** were found to be inactive against pathogens with an efflux gene (mef) and against pathogens with a constitutively resistant *S. pyogenes*. New azithromycine sulfonamide conjugates **65a** and **65b** exhibit somewhat lower activity than **azithromycin** against sensitive *S. pneumonia* (MIC, 0.5 and 1 mg/ml, respectively) and *S. pyogenes* (MIC, 2 mg/ml) strains. Furthermore, **65c** and **65d** showed in general lower activity against most of the tested bacterial strains except for sensitive *S. aureus* and *M. catarrhalis* where better activity was observed in comparison with **65a** and **65b** analogs. All **azithromycin** sulfonamide conjugates **65a-65d** (Fig. **26**) are inactive against Gram-negative *H. influenzae* and *E. coli* strains [66].

Compounds **66** and **67** (Fig. **27**) showed significant antibacterial activity against *E. coli* and *S. aureus*, while they were found to show moderate activity against *S. typhi*, *P. aeruginosa* and *Pneumococci*. The most active compounds were **66b**, **66c**, **67b**, **67c**, and **67e** against both *E. coli* and *S. aureus*, which were approximately equipotent in activity and comparable to that of sulfamethoxazole and Norfloxacin at all concentrations. Both the reference drugs exhibit antibacterial activity by inhibiting dihydrofolate reductase and bacterial DNA gyrase, respectively. The antibacterial activity exhibited by **66b**–**d** against *S. aureus* was more than that against *E. coli*. Compounds **67b**, **67c** and **67e** showed superior activity against *S. aureus* even at 50 μg concentration. From the results, it is evident that the presence of a 5-guanylhydrazone and 5-thiocyanato group resulted in producing good anti-bacterial activity. Particularly, **67b** *para*-chlorophenyl, **67c** *para*-bromophenyl and **67e** *para*-nitrophenyl derivatives showed increased activity. All these compounds can be considered as potential candidates for anti-bacterial activity against both Gram-positive and Gram-negative organisms [67].

4. ANTI-INFLAMMATORY SULFONAMIDES

1,3,5-trisubstituted pyrazolinesulfonamide derivatives given in (Fig. **28**), while compounds **68c** and **68e** showed maximum anti-inflammatory activity having no ulcerogenic effects which is equal to that of standard drug **celecoxib**. Hence, therefore acute toxicity study of **68c** and **68e** showed that these are well tolerated up to 100 mg/kg orally. On the other hand, compounds **68c** and **68e** showed very mild inhibition against the enzymatic activity of cyclooxygenase COX-1 and COX-2. Compounds **68c** and **68f** exhibited considerable anti-cancer activities against the entire tested tumor cell lines. Specifically, compound **68f** showed prominent anti-proliferative activity with GI_{50} values less than 2 μM particularly against MOLT-4 (1.94 μM), SR (1.28 μM) in leukemia cancer, EKVX (1.88 μM) in non-small cell lung cancer, and COLO 205 (1.69 μM) in colon cáncer [68].

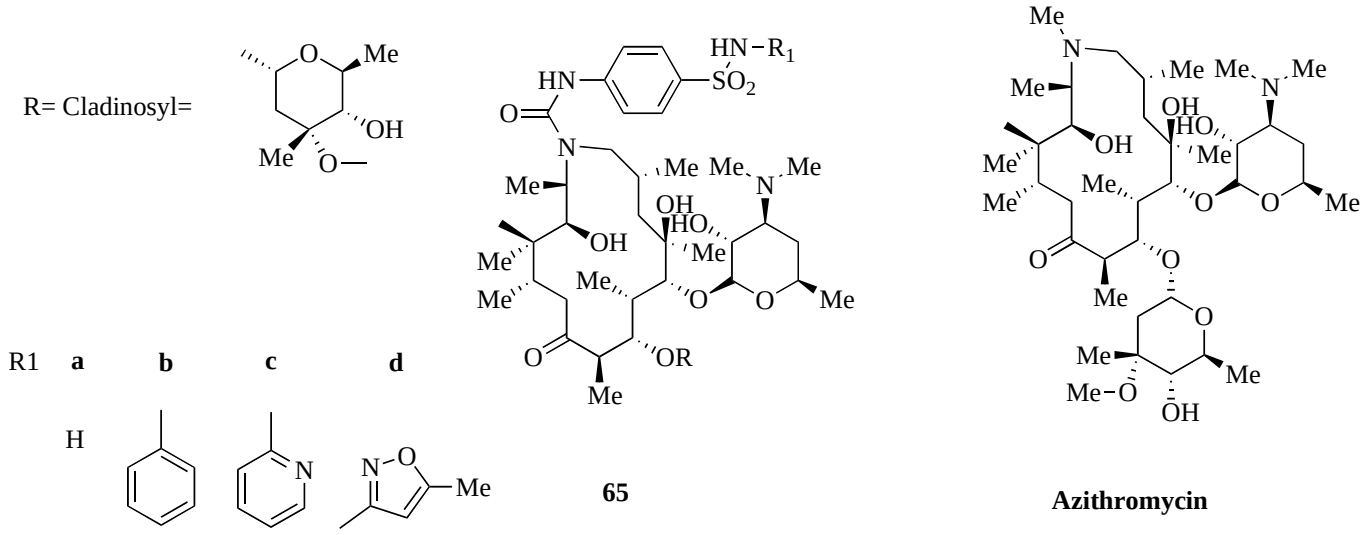
Compounds **69a**, **70f** (at 100 mg/kg p.o.) and **69b**, **69d-g**, **69i**, **70a**, **70b**, **70d**, **70g**, **70i** (at 50 mg/kg p.o.) (Fig. **29**) exhibited 20, 12, 34, 16, 44, 21, 11, 20, 31, 20, 37, 25 and 13%, anti-inflammatory activity whereas the standard drug



64

a Z= N, n= 1, R= CH_3 R1= R2 = H
b Z= N, n= 1, R= C_2H_5, R1 = R2 = H
c Z= N, n= 1, R= H, R1 = CH_3, R2 = H
d Z= N, n= 1, R= H, R1 = R2 = CH_3
e Z= N, n= 1, R= R1 = R2 = H
f Z= N, n= 1, R= Bn, R1 = R2 = H
g Z= O, n= 1, R1= R2 = H
h Z= N, n= 2, R = R1 = R2 = H
i Z= N, n= 2, R= CH_3, R1 = R2 = H

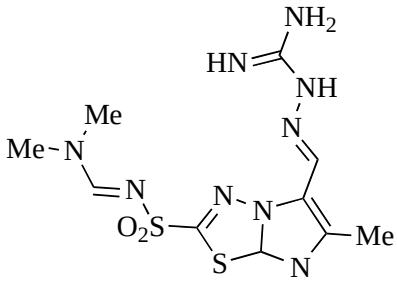
Fig. (25). lb-methylcarbapenems having cyclic sulfonamide moieties.



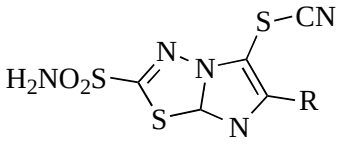
65

Azithromycin

Fig. (26). Structure of compounds 65a-d and azithromycin sulfonamide conjugates as inhibitors of resistant *Streptococcus pyogenes* strains.



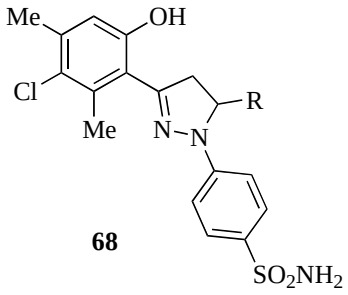
66



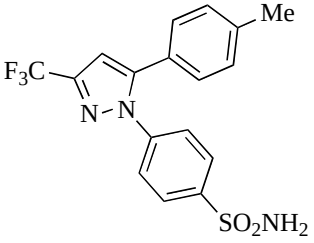
67 a-d,f

a, R= C_6H_5; **b**, R= 4-ClC_6H_4
c, R= 4-BrC_6H_4; **d**, R= 4-$CH_3C_6H_4$
e, R= 4-$NO_2C_6H_4$; **f**, R= 3-coumarinyl

Fig. (27). 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives.



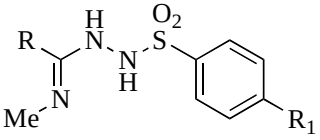
68



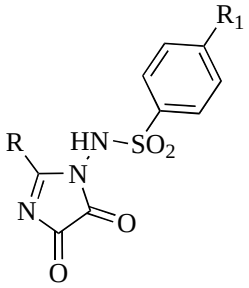
Celecoxib

a R= Phenyl
b R= 4-Methoxyphenyl
c R= 4-Chlorophenyl
d R= 2-Chlorophenyl
e R= 2-Hydrohyphenyl
f R= 4-(*N*,*N*-dimethylamino)phenyl
g R= 3,4-Dimethoxyphenyl
h R= 3,4,5-Trimethoxyphenyl

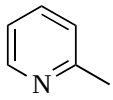
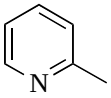
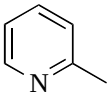
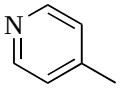
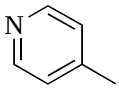
Fig. (28). Pyrazole sulfonamides derivatives and celecoxib with anti-cancer and anti-inflammatory activity.



69



70

	R	R1
a		Me
b		OMe
c		H
d		H
e		OMe

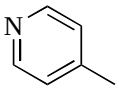
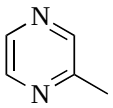
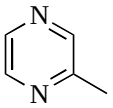
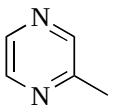
	R	R1
f		OMe
g		H
h		Me
i		OMe

Fig. (29). *N*-methyl derivatives of amidines and cyclized five-membered products of amidines with oxalyl chloride.

phenylbutazone showed 58% (at 100 mg/kg p.o.) and 37% (at 50 mg/kg p.o.) anti-inflammatory activity. Therefore, compound **69e** showed anti-inflammatory activity which is better than the standard drug. Results indicate that in case of N-methyl derivatives of amidines replacement of 2-pyridyl or 2-pyrazinyl group by 4-pyridyl was found to be useful for anti-inflammatory activity. On the other hand, anti-inflammatory activity decreases when CH_3 group on phenyl ring was replaced by -OCH_3 while it increases when there is a substitution by -CH_3 on phenyl ring, i.e compound **60e**. This could be due to change in electron richness of phenyl ring and steric crowding. Particularly, compound **69a** exhibited better analgesic activity and any change in phenyl ring or of 2-pyridyl to 4-pyridyl or 2-pyrazinyl decreased the analgesic activity. In case of cyclized compounds, i.e **70a-i**, 4-pyridyl derivatives showed good anti-inflammatory activity as compared to 2-pyridyl or 2-pyrazinyl derivatives [69].

In summary, sulfonamide is a very important scaffold to design new compounds with potential biological activity, particularly as anti-tumoral, antibacterial and anti-inflammatory agents, that could be more promissory that sulfa drugs that we know.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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