

Small Molecule Drugs; Down but Not Out: A Future for Medical Research and Therapeutics

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Abstract: Small molecules are intracellular targeting; low but variably specific (predominantly) organic substances with well-defined structures and molecular weight of less than 900 Daltons that help regulate biological processes mainly by metabolic degradation. Differences in size, make, pharmacokinetics, pharmacodynamics and suitability for certain drug forms over others confer certain advantages on small therapeutic molecules over large ones or biologics. Though biologics, aided by biotechnological revolution, target specificity and efficacy are favored ahead of small molecules in current medical research. However, global rise in disease and multidrug resistance (MDR) of pathogens means biologics alone are not enough in the race against diseases and infections. In this review, a case is made for more investigation of small molecules in in-vivo and in-vitro therapeutic assay screenings. Also, other small molecules are highlighted, both organic and synthetic, that have proven medicinal capabilities. Finally, we confer some advantages inherent in small molecule therapeutics so as to provide a better view for the development of new drugs and the future direction of medical therapeutics.

Keywords: Therapeuticity, small molecule, assays, biologics.

I. Introduction

Over the years, boom in biotechnology have given rise to biomacromolecular drugs that have contributed immensely to combating various diseases and ailment. Currently, these biologics possess amazing specificity and efficacy that have revolutionized the medical world. Despite these advantages, biomacromolecules never formed the bedrock of medical research and therapeuticity. Small molecule drugs did. In short, the first set of medically employed drugs were small molecules, mainly natural products or extracts, which were screened in whole organism to fish out those with required therapeutic benefits in a classical pharmacological process. Today, these small yet effective allies are being ignored in pursuit of their bigger neighbors. What then are small molecule drugs? These are intracellular targeting, low and variably specific drugs, usually organic substances with well defined chemical structures and molecular weight of less than 900 Daltons, that help regulate biological processes mainly by metabolic degradation [89, 92]. Apart from size, small molecule drugs differ from biologics in terms of clearance mechanism, dosage regimen, metabolism, reactivity, target spectrum, distribution and molecular interactions. With astronomical rise in global burden of disease and multidrug resistance (MDR) of pathogens, 'biologics revolution' has not lived up to expectation in terms of meeting up with increasing demand for drugs and disease control. In same vein, medical research especially in developing nations is dwindling because poverty coupled with corruption have made acquiring sophisticated biotechnological equipment needed for biologics research herculean task. In this review, we make a case for more investigations of small molecules in in-vivo and in-vitro therapeutic assay screenings. We also highlight other small molecules, both organic and synthetic, that have proven medicinal capabilities in literature to buttress our point. Finally, we confer some advantages inherent in small molecule therapeutics over those with bulky molecular structures, which are currently preferred in therapeutic assays, so as to provide a better view for the development of new drugs and the future direction of medical therapies in developing nations.

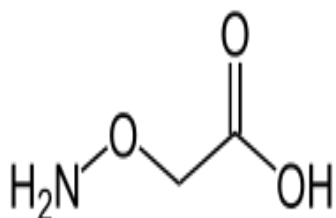
II. Small Molecules

Many small molecules have been employed for different medical therapeutic uses over the years with great success. From the most dreaded diseases like cancer, diabetes, epilepsy, obesity etc to more humane ailments of cough, fever, cold amongst others. Some of these molecules have been abandoned due to various reasons, while others have suffered neglect due to lack of *medical cum scientific viability*. Many others are still in use, howbeit, with less enthusiasm when compared to their bio-technologically driven contemporaries, *biologics*. Though the

list is endless, here are few small molecules with experimentally (and clinically) proven pharmacological efficacy.

2.1. 2-Aminooxyacetic acid

2-Aminooxyacetic acid usually abbreviated AOA or AOAA, is a derivative of hydroxylamine. As a molecule, it has been found to be a potent competitor inhibitor of the enzyme γ -aminobutyric acid- α -ketoglutaric acid transaminase derived both from *E. coli* and mammalian brain [1, 67]. At optimal inhibition level in various regions of the rat brain, 4-aminobutyrate aminotransferase activities, aminooxyacetic acid is regarded as a useful tool to study regional gamma-aminobutyric acid (GABA) turnover in rat models [2, 68, 69].

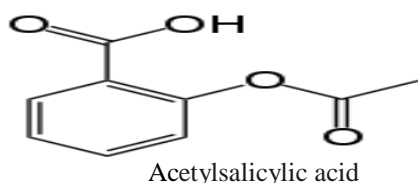


2-(aminooxy)acetic acid

Generally, AOA inhibits pyridoxal phosphate (PLP)-dependent enzymes, including GABA [3], by attacking the Schiff base linkage between PLP and the enzyme, forming oxime-based complexes [3]. AOA inhibits aspartate aminotransferase, another PLP-dependent enzyme, which is an essential part of the malate-aspartate shuttle [4]. The inhibition of the malate-aspartate shuttle prevents the re-oxidation of cytosolic NADH by the mitochondria in nerve terminals [4]. Also in the nerve terminals, AOA prevents the mitochondria from utilizing pyruvate generated from glycolysis, thus leading to a bioenergetic state similar to that of hypoglycemia. [4] AOA has been shown to cause excitotoxic lesions of the striatum, similar to Huntington's disease, potentially due to its impairment of mitochondrial energy metabolism [5]. Clinically, AOA was used to reduce symptoms of Huntington's disease by increasing GABA levels in the brain though at concentration beyond 2mg per kg per day, patients who received the AOA treatment failed to show clinical improvement and suffered from side effects such as drowsiness, ataxia, seizures, and psychotic behavior.[6] Also, the inhibition of aspartate aminotransferase by AOA has clinical implications for the treatment of breast cancer, since decrease in glycolytic rate disrupts breast adenocarcinoma cells more than normal cells [7]. AOA has been studied as a treatment drug for tinnitus [8, 9, 10]. One study showed that about 20% of patients with tinnitus had a decrease in its severity when treated with AOA, though side effects mostly nausea and disequilibrium were reported. [10]; we opine that establishing mechanisms to completely remove these side effects can open a new window of scientific research involving AOA, since its biomedical usefulness is not in doubt. Furthermore, AOA acts as a convulsant agent in mice and rats at high concentrations [11, 12, 68]. AOA has also been shown to increase the vase life of cut flowers by inhibiting 1-aminocyclopropane-1-carboxylate synthase preventing ethylene synthesis [13, 14].

2.2. Acetylsalicylic acid

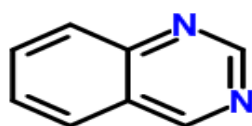
Acetylsalicylic acid normally called aspirin with formula of $C_9H_8O_4$ has 180 molecular mass. Its IUPAC name is 2-acetoxybenzoic acid. It has anti-platelet effect, by reducing blood clotting by regulating number of platelets in the blood through production of platelet binding thromboxane. It is one of the most medically employed salicylated drug all over the world used to prevent heart attacks, strokes and for patients with blood clotting challenges [71]. Subsequent dosage of aspirin immediately after heart attack has been shown to avert further cardiac arrest or damage of cardiac tissues [72, 74]. Its potentials against colorectal cancer have also been enunciated [73, 75, 76]. Though side effects have been reported at higher doses. Recent results suggested that aspirin also possess verified therapeutic potentials against coronary heart disease [77,78, 88], kawasaki disease [79], breast cancer [80], and pre-eclampsia [81-86, reviewed in 87].



Acetylsalicylic acid

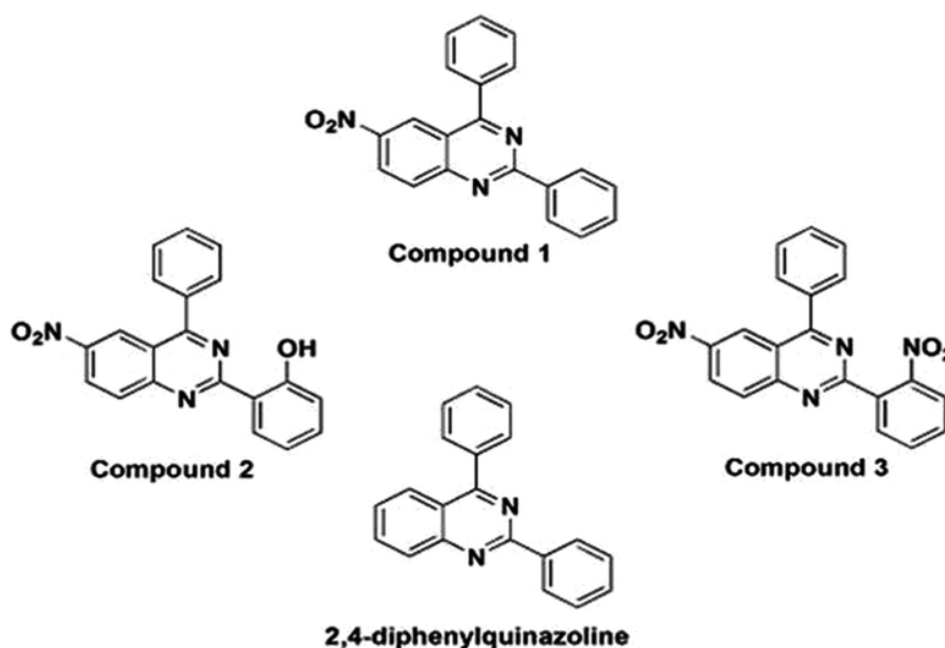
2.3. Quinazoline and Quinazolines

Quinazoline with chemical formula $C_8H_6N_2$ is a heterocyclic compound made up of two fused six-membered simple rings; benzene and pyrimidine rings. Many therapeutic applications of quinazoline and its analogs (Quinazolines) have been studied. PD 069185, trisubstituted quinazoline; is a highly selective and structurally novel inhibitor of endothelin converting enzyme-1 [15]. With an IC_{50} value of $0.9 \pm 0.1 \mu M$ for inhibition of human ECE-1 from the solubilized membrane fraction of CHO cells stably transfected with human ECE-1 cDNA, Ahn et al reported that PD 069185 is best fit with a competitive inhibition model with a K_i value of $1.1 \pm 0.1 \mu M$ and binds in a reversible manner [15]. In addition, they inferred that PD 069185 at 200–300 μM has little effect on other metalloproteases, such as neutral endopeptidase 24.11, stromelysin, gelatinase A, collagenase, suggesting a high ECE-1 specificity, and thus has the potentials of serving as a valuable tool to study the pathophysiological role of endothelin and the therapeutic potential of ECE-1 inhibitors. Doxazosin mesylate is a quinazoline compound used for treating High Blood Pressure and Benign prostatic Hypertrophy [16]. Clinical effects of kidney-tonifying and dampness-expelling Chinese herbal medicine combined with doxazosin in the treatment of chronic epididymitis in human patients have also been reported [17].



Quinazoline [15]

Three quinazoline based small molecules, having core structural moiety of 2,4-diphenylquinazoline, was reported to have showed global upregulation of miRNA expression with a selective enrichment of tumor suppressor miRNAs, thus present picture of scaffolds necessary for designing activators of miRNA expression paving the way for novel anti-cancer drugs [93].

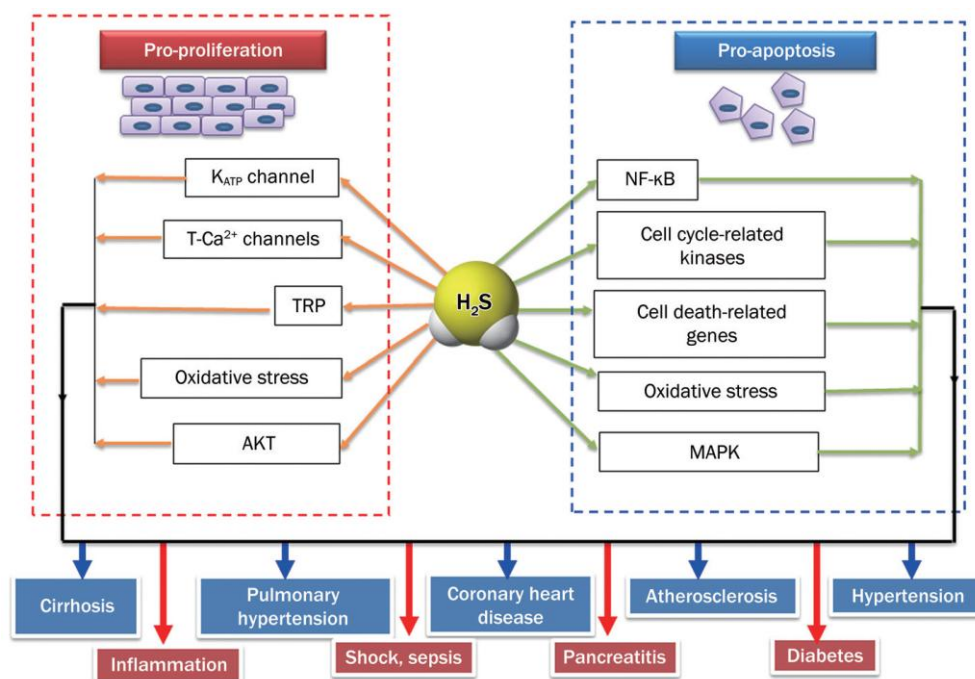


2,4-diphenylquinazoline based compounds with potential anticancer possibilities [93].

2.4. Hydrogen sulphide and related compounds

H_2S is an acidic gas that gives rotten eggs its foul smell. It is one of the principal components of natural sulphur cycle. Direct sulfate reduction and protein metabolism by bacteria and fungi are the natural principal ways through which it is released into the environment. Till recently, H_2S has been regarded as a mere gaseous environmental pollutant. Scientific research in past few years has re-activated a renewed interest to the therapeutic abilities of H_2S . Onion, garlic, leek and chive are known to possess medicinal properties. Evidences suggest that these antioxidant properties are due to its hydrogen sulphide content [18, 19, 20]. Anti-cancer and anti-diabetic applications of garlic, most especially, have been reported extensively in literature [21, 22, 23, 19].

H₂S has also been implicated as a signaling molecule in endogenous neuromodulation [24]. Localized increase in H₂S was reported to have attenuated the aggravation and exacerbation of symptoms in AD human patients by guiding against amyloid β-induced cell cytotoxicity in central nervous system [25, 26, 27], just as its protective and regulatory roles have been enunciated in hypertensive (28, 35), atherosclerotic [29, 30], diabetic [31] and ischemia reperfusion injuries [32, 33, 34, 21, 38, 41, 43] in mouse models. Interestingly, H₂S and many donors of H₂S are known and have been medically investigated to possess varying degrees of therapeutic potentials in many ailments including cardiovascular diseases [35, 39, 40], memory impairments (36), inflammations /stomach disorders [37, 42, 47, 51, 52], circulating gasotransmission [48], ion signaling [49] etc. Recent studies also suggested that H₂S could represent a unique biomarker in patients affected with hyperhomocystinemia to define the susceptibility of a cardiovascular events driven by platelets [70]. In other reports, H₂S in conviviality with other molecules especially Nitric oxide have shown proven potentials in medical investigations especially in tumor/cancer therapy [44, 45, 46]. As propounded by Khosrow et al [53], the potential applications of H₂S can be summarized diagrammatically as shown below, though they do have side effects but that on its own can open virgin fields of medical research and applications.



Potential involvement and application of the targets of H₂S, including observed dual effects [53].

2.5. Fluorine and fluorinated molecules

Fluorine (F), atomic number 9, is a chemical element and lightest halogen known. It is highly electronegative, extremely reactive and exists as a diatomic, yellowish gas at standard conditions. The usefulness of fluorine in medicinal chemistry is well documented. Indeed, an avalanche of fluorinated drugs exists in today's market. Generally, it is known that fluorine replacement of hydrogen or oxygen in C–H or C–O bonds has unique merits in biologically active molecules; of special mention is the application of fluorination reactions to increase metabolic stability in drug designing. Much fluorine-based and fluorinated drugs have been applied for treatment of innumerable health challenges. Metabolic disorder arising from malfunctioning of diseased organs such as liver, pancreas, leading to abnormal chemical reactions and disruption of normal body metabolic timetable has attracted the application of fluorinated drugs in generating many effective therapies and promising leads. Anti-diabetic drug research has concentrated mainly on biological targets. Some of such drugs include Sitagliptin [54], a dipeptidyl peptidase IV inhibitor, which helps to prolong the beneficial effects of Glucagon-like peptide 1 on glucose homeostasis by stimulating the biosynthesis of insulin as well as inhibition of glucagon release in living systems. CP-320626 is another fluorine-based drug that is reported to function as a liver glycogen phosphorylase inhibitor in synergy with glucose by allosteric binding [55], while oral administration of T-226296 in mouse models led to complete suppression of intracerebroventricular-injected Melanin-concentrating hormone receptor thus functioning as a potential anti-obesity agent [56–59], and treatment of depression and anxiety. Fluorine-based drugs with therapeutic potentials against cardiovascular diseases have also been reported in literature [60–65].

III. Merits Of Small Molecule Therapeutics

Small molecules are intracellular targeting, low and variably specific, usually organic substances with well defined structures and molecular weight of less than 900 Daltons that help regulate biological processes [89]. As suggested in the definition above, differences in size, make, pharmacokinetics, pharmacodynamics and suitability for certain drug forms over others confer certain advantages on small therapeutics over large ones or biologics. For a start, classical drug development works with small, chemically manufactured active substance molecules. For instance aspirin, discussed above, is an active ingredient with a molecular weight of about 180 Da. As an advantage, these small molecules can be processed into easily ingestible tablets or capsules. If soluble within gastrointestinal tract environment, the dissolved active substance is absorbed into the systemic circulation via the intestinal wall. Consequent dispersal into the desired destination in the body is easy because of their tiny size. Moreover, small structure and chemical composition also aid their easy penetration into cell membranes or target organs thus conferring an intra-cellular advantage over extracellularly oriented, highly specific biological proteins. Small molecules, therefore, have a broader spectrum target, unlike biologics that are characterized by high selectivity for their target molecules. Similarly, small molecules are easier to synthesize, which is simply by chemical interaction between different organic and/or inorganic compounds. The implication is that small but therapeutically active substances for therapeutic applications can be synthesized in research laboratories employing the familiar round-bottom flasks and rotary evaporators, found commonly all around the world. Thus high-throughput screening search for small molecules which can be used as lead compounds for new drugs can be done anywhere. This is particularly important for researchers in third world countries where sophisticated machines for large molecular synthesis and screenings are obviously not available. Accepted that biologics possess impregnable efficacy and high tolerability, however, poor long term adherence due to injection/infusion phobia is very common. In a recent research, needle phobia was found to prevent patients from self-injecting their biologics [90], just as other survey reported that twenty-two percent of a population sample agreed to have injection phobia/ needle fear [91]. Interestingly, injection risks, ignorance of injection pain management and associated side effects are always major concerns of such non-compliance. Small molecules, on the other hand, are majorly administered orally implying that non-compliance arising from such fears as elucidated above is predominantly averted. Orally administered therapeutics has the potentialities to increase treatment regimen, up-regulate patient satisfaction and adherence; and consequently improve efficacy. Furthermore, small molecules generally possess short half lives but longer shelf lives when compared to larger neighbors; biologics. In cases where rapid metabolism is of necessity, for instance during infectious disease outbreaks or surgeries, short half-lives of small molecules might be of substantial therapeutic benefit. Speculatively, small molecules might possess economic advantage since they require less complex processes and less rigorous manufacturing processes. Also, higher accessibility by patients is possible especially in local areas where infrastructure is lacking and professional administrators are few.

IV. Authors' Concluding Remark

In this review, we attempted to make a case for more direct involvement of small molecules in therapeutic studies. We highlighted drugs with proven medical potentialities, yet of small molecular weights, to buttress our points. Arguably, we have not compared or discarded biologics in our argument for small molecules, as they are dependably effective in extracellularly targeted therapies, as well as, highly selective for individualized medications. On the other hand, we aver that their easy ingestibility, high possibility of oral administration, broader spectrum, screening convenience, accessibility to patients and economic implications are special advantages that can be harnessed by researchers in exploiting small molecules for medical researches and applications. It is our wish that medical, biological scientists and related professionals can be inspired to exploit the opportunities presented by small molecules as therapeutics. Who knows if the solution to world's most dreaded ills lies in small atoms that we ignore daily?

Acknowledgement

To God be the Glory!

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