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Sharing via Low-Cost Discovery in Global Effort for Combat Diseases: Simple Chemical Routes for Lead Compounds Using Biomass Driven Building Blocks

Galal A. M. Nawwar*, Randa H. Swellam and Hoda S. Othman

Green Chemistry Department, Chemical Industries Research Division, National Research Centre, Al Buhouth St., Dokki, Giza, Egypt PO box 12622, Dokki, Giza, Egypt.

AMONG various participations in the global efforts for drugs, preservatives and pesticides discovery, there are cost-effective simple synthetic routes via productive methods to synthesize potent biologically active compounds, utilizing biomass driven starting compounds. This eco-friendly approach appropriates also researchers where shortage in research fund and facilities. Versatile precursors such as 3-oxoalkane carboxylates, activated nitriles and a,β unsaturated ketones, were utilized for the facile synthesis of various biologically interesting small molecules. In this review, we highlight representative synthetic findings for bioactive leads arising from our continuous attempts with this approach. Further development by industry and academia through lead optimization will produce new active ingredients to face contiguous hazard biological challenges and resistance of microbes and insects. Many other researchers have made many great achievements in each of these subjects, but these are beyond the scope of this review.

Keywords: Sustainability, Biomass, Organic synthesis, Bioactive small molecules.

Introduction

It is clearly appeared beyond doubt that research plays a significant role in shaping the societies' future as never before. One of the problems for most African regions, for example, is the poor quality and quantity of research-based education, as well as low level of research funding. Hence, African researchers produce only around one percent of the world's research [1]. Research and discoveries allow universities to better serve their respective societies, and result in direct benefits, fuelling economic growth. A new report from the World Bank and science publisher Elsevier looked at Africa's research performance over this last decade, and shows that the quality and quantity of that research is improving [2]. The report concludes by recommending that African governments should accelerate support to research in Africa to build the necessary human capital to solve African problems. In addition, many African students leave their countries to study at universities in Europe, Asia and America and do not return [3,4]. Thus, existing African scientific communities need to be nurtured. In this context, different research scenarios should be tested and polarized to overcome obstacles facing development through applying research.

Synthetic approaches utilizing biomass represents an important alternative to the non-sustainable fossil resources in producing chemicals and fuels, at the same time that the interest in the environment increases and search for new active ingredients needs extensive multidiscipline research and huge fund [5]. Particularly, plant-derived biomass is a reproducible and low environmental-loading resource, produced from CO_2 and water via photosynthesis using sunlight [6,7]. Biomass, including cellulose, lignin and chitin, represents the most abundant renewable carbon resource on the earth and could offer a wide platform of starting compounds and substrates for the production of bulk and specialty chemicals [5], that help researchers especially in developing countries to use them and discover new bioactive small molecules to participate in the global efforts for discovery new drugs, food preservatives, and pesticides (cf. Fig.1) [8].

*Corresponding author e-mail: gnawwar@yahoo.com
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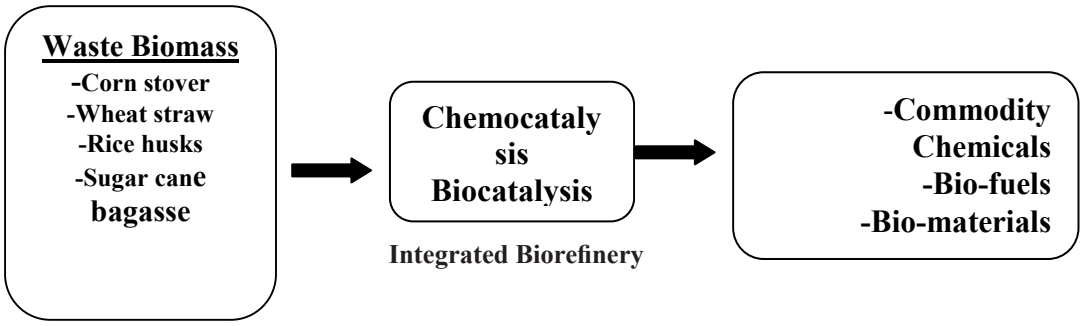


Fig.1. The bio-based economy.

Cellulose for example, is a polymer of glucose units linked by β-1,4-glycosidic bonds. It could be easily hydrolyzed affording glucose which considered a versatile precursor to valuable chemicals such as biodegradable plastics and ethanol (cf. Fig.2) [6].

Hence, the conversion of cellulose has attracted world-wide interest. Catalytic conversion of biomass into glucose, polyols, 5-hydroxylmethyl furfural (HMF), alkyl glucosides and aromatic compounds have been extensively studied. Meanwhile, transformations of biomass into valuable organic acids including lactic acid, levulinic acid, formic acid, acetic acid and gluconic acid have also received considerable attention. These acids, especially, ranging from C1 to C6, play a vital role in the industry of chemistry as a food additive, and a key industrial chemical for polyvinyl acetate and synthetic fibers production [5]. In this context, Hemicelluloses, types of plant cell wall polysaccharides also can be easily hydrolyzed into pentose (xylose and arabinose) and hexose (glucose, galactose, and mannose), and transformed into fuel ethanol and other value-added chemicals, such as 5-hydroxymethylfurfural (HMF), furfural, levulinic acid, and xylitol [9].

It's worth to mention that, among reasons that make giant firms searching for bioactive molecules discovery interested in active compounds driven from this simple synthetic approach, are almost ease of products purification, high products yield, absence of reaction side products. Additional reason for this interest is the simple technological facilities needed for their industrial scale production. There is a considerable number of approved biomass driven drugs in the market as well as compounds currently going through different clinical phases or registration statuses [10].

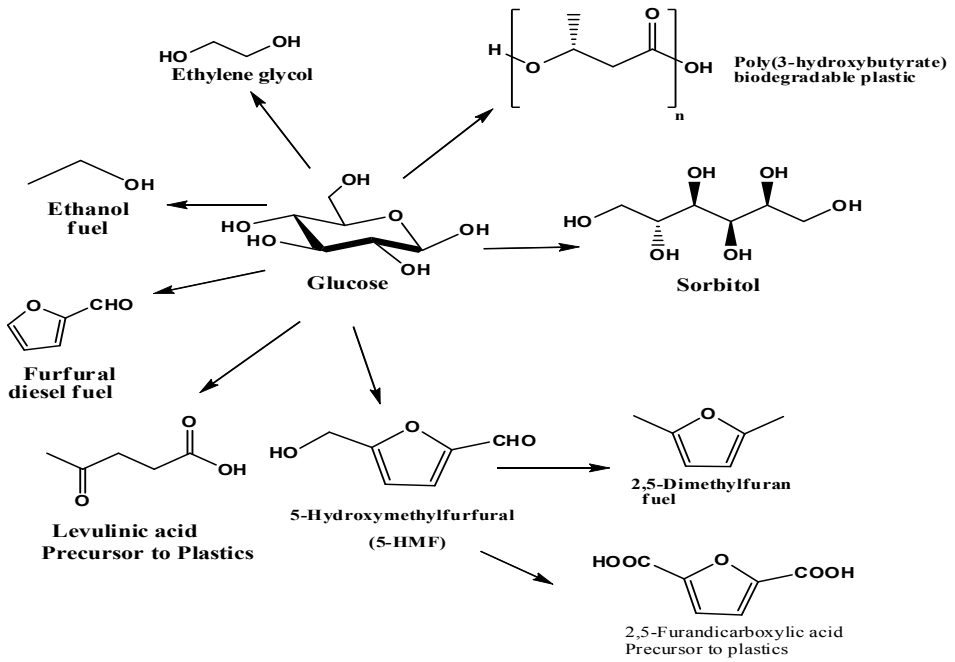


Fig.2. Derived chemicals from glucose.

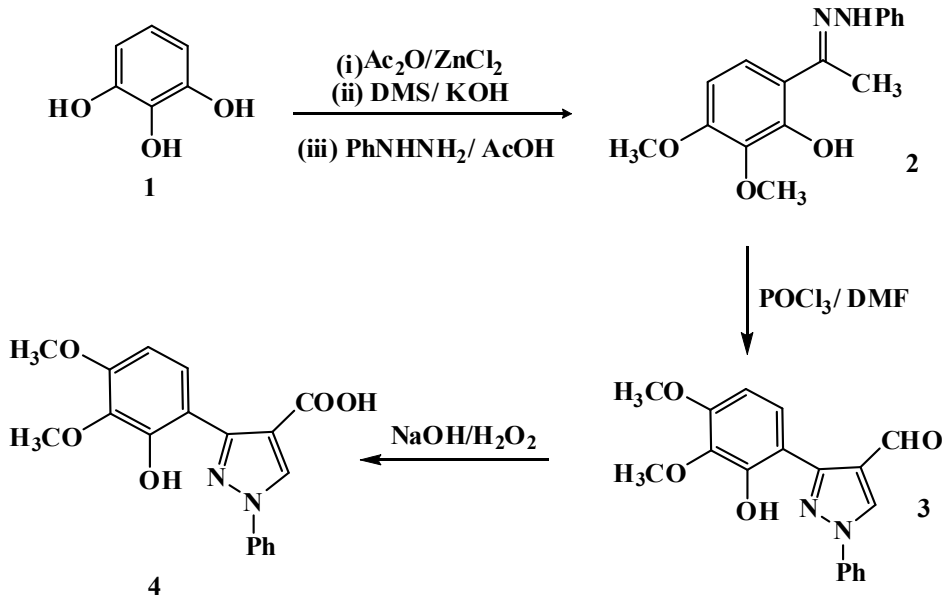
Infectious diseases, which scientists combat by bioactive small molecules among other several tools, are the most leading causes of human morbidity and mortality for most of human existence. Over the past three decades, our research program has been centered on seeking simple synthetic chemistry that can drastically increase efficiency toward low cost-discovery and sustainability. This review focuses on discovering chemistry that can directly and efficiently utilize natural feed stocks without extensive derivatization. This review briefly summarizes our efforts in the synthesis of antibacterial, antifungal, antitumor, Analgesic and anti-inflammatory, antioxidants besides insecticides and molluscicides lead molecules in an attempt to participate in the global effort to combat diseases. It is worth to mention that the poly functionality of the presented lead structures in this review facilitates their chemical transformation for the lead optimization study.

A) *Simply synthesized lead antibacterial compounds*

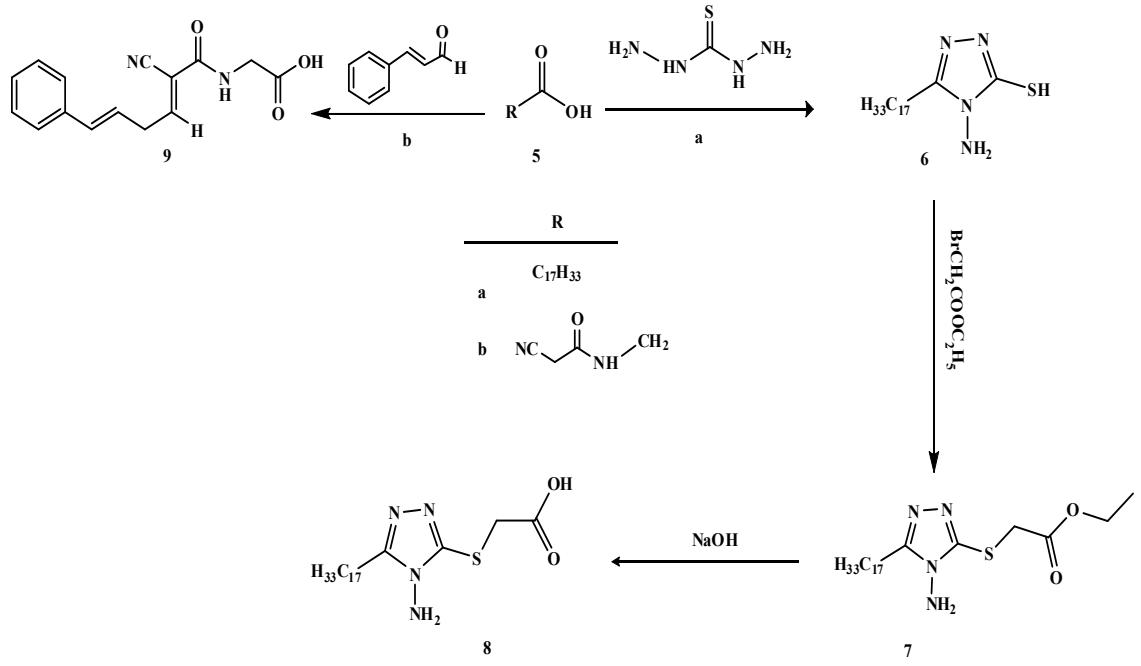
Antibacterial agents are compounds or substances that kill or slow down the growth of bacteria, they save countless lives and make enormous contribution to the control of infectious diseases since the beginning of antibacterial era [11]. Antibiotics perturb important bacterial biochemical processes, and they can be classified based on the cellular component or system they affect, in addition to whether they induce cell death (bactericidal drugs) or merely inhibit cell growth (bacteriostatic drugs). Most current bactericidal antimicrobials inhibit DNA synthesis, RNA synthesis, cell wall synthesis, or protein synthesis.

During recent years, the overuse and misuse of antibiotics stimulated the more rapid emergence of antibiotic-resistant bacteria (ARB) and antibiotic resistant genes (ARGs), reducing their therapeutic potential against human and animal pathogens [12]. World Health Organization characterizes antimicrobial resistance as growing public health threat of broad concern to countries and multiple sectors that must be managed with the utmost urgency [13]; situation caused the need for developing new and potent antimicrobial agents. In this attempt, we utilized pyrogallol, from biomass driven gallic acid, to synthesize a series of pyrazoles containing gallate moiety. These pyrazoles were tested for antibacterial activity and the obtained data revealed that compound **4** showed a comparable effect to a well-known antibacterial agent [14].

Glycine, cinnamaldehyde and oleic acid also are biomass driven building blocks. They were utilized in the synthesis of the most effective antibacterial agents **8** and **9** among several synthesized and tested compounds [15, 16].



Scheme 1: Utilization of pyrogallol in the synthesis of lead antimicrobial pyrazole.



Scheme 2: Glycine, Cinnamaldehyde and oleic acid as precursors for synthesis of potent antibacterial (8).

Terephthalic acid obtained from recycling of plastic bottles waste (PET)was utilized to synthesize 1,3,4-Oxadiazole **13** which showed high antibacterial activity [17].

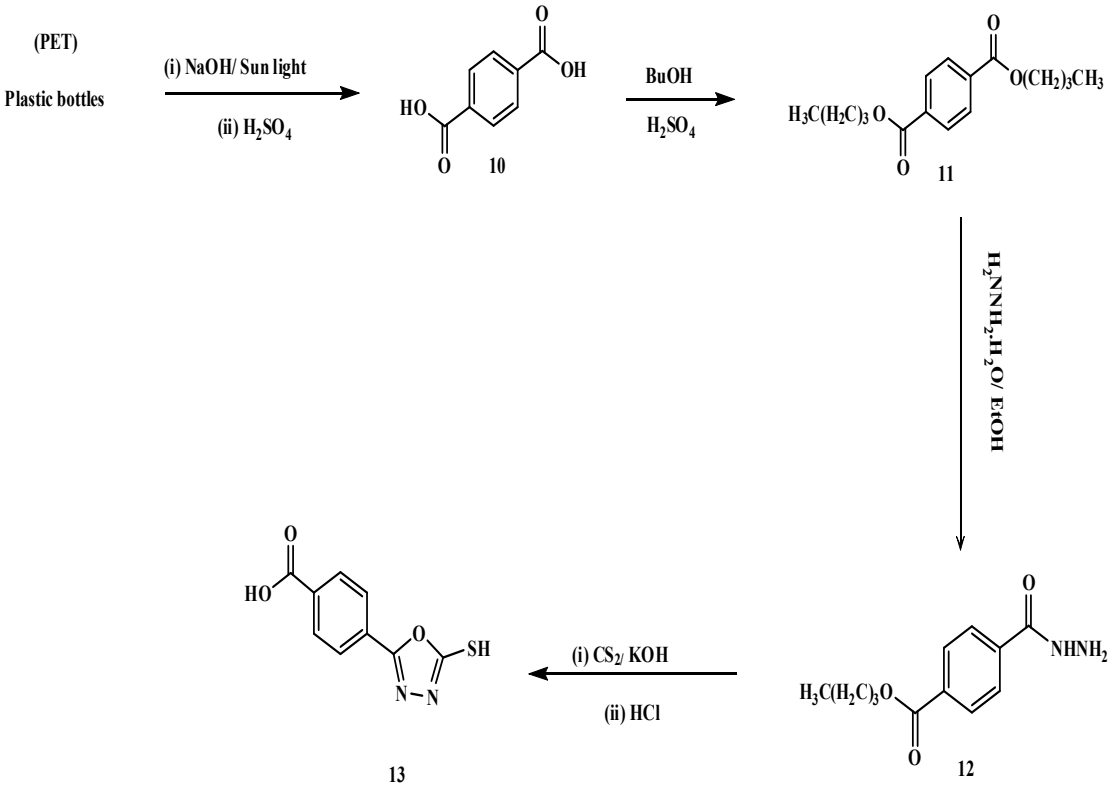
B)Facile synthesized lead Antifungal compounds:

Fungi Kingdom is one of the most diverse groups of organisms on Earth[18]; it includes some of the most important organisms, both in terms of their ecological and economic roles. By breaking down dead organic material, they continue the cycle of nutrients through ecosystems. In addition, most vascular plants could not grow without the symbiotic fungi, or *mycorrhizae*, that inhabit their roots and supply essential nutrients. Other fungi provide numerous drugs (such as penicillin and other antibiotics), foods like mushrooms, truffles and morels, and the bubbles in bread, champagne, and beer. Although there are millions of different fungal species on Earth, only about 300 of those are known to make people sick. They became important human pathogens only in the late 20th century, primarily in hosts with impaired immunity as a consequence of medical interventions or HIV infection [19].

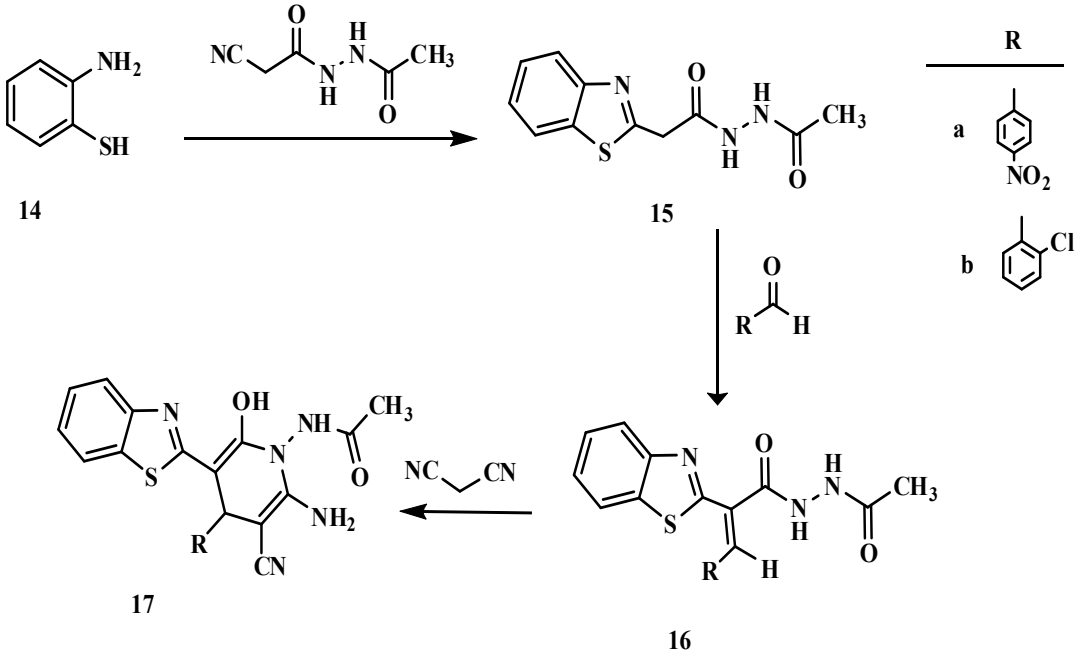
In the past few decades, a worldwide increase in fungal infections has been observed with a rise in the resistance of some species of fungi toward different fungicides used in medicinal practice [20]. *Candida albicans* (*C. albicans*), an example of resistant fungus to antifungal agents, is the most common fungal pathogen in clinical settings and is responsible for infections that can affect the skin and the mucosa or cause life-threatening systemic disease [21]. The mortality among patients with invasive candidiasis is as higher than 40%, even when patients receive antifungal [22]. Therefore, it is important to find new antifungal agents especially that are driven from biomass.

One of our trials to do so is the utilization of acetic acid which is produced from biomass refining or fermentation. Its derivatives, for example, ethyl cyanoacetate and cyanoacetic acid are important building blocks in organic synthesis. Thus, Arylidine derivative **16a** and 3-(benzothiazol-2-yl)dihydropyridine**17b**, simply synthesized from *N*-acetylbenzothiazol-2-yl-acetohyrazide **15**, exhibited remarkable antifungal activity [23].

In continuation, compounds **22a,b** showed remarkable fungicidal activity. They were synthesized by the reaction of triazole **18** or triazine **19** with ethylcyanoacetate via addition with subsequent self-cyclization to afford **20**. Compound **20** was successfully added to carbon disulphide to produce compound **21** in good yield. Finally, potent fungicide **22** could be obtained from the reaction of **21** with hydrazine hydrate [24].



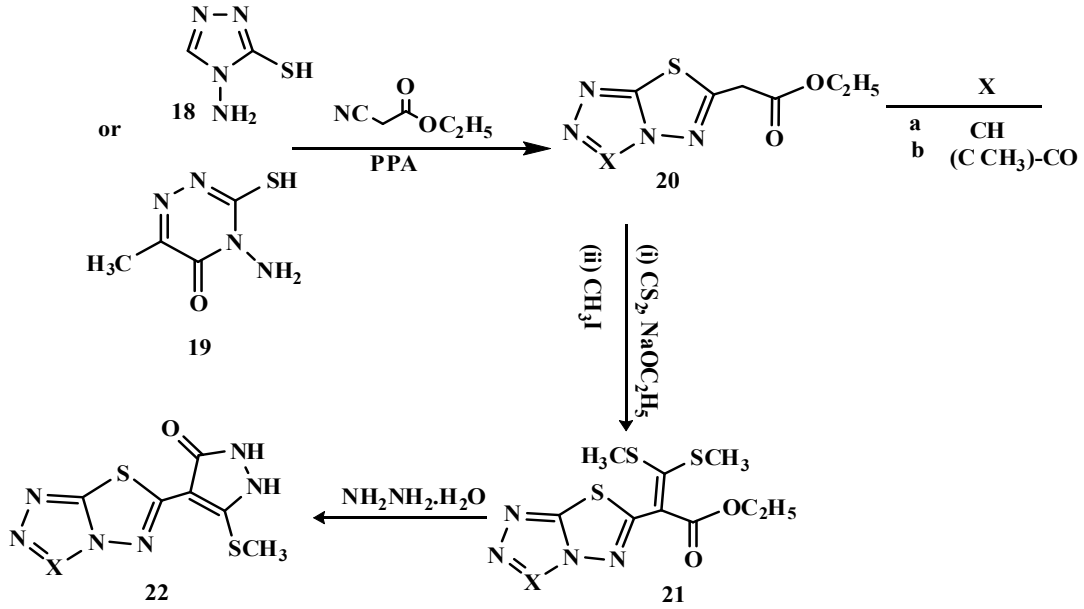
Scheme 3: Recycling of plastic bottles to synthesize lead antibacterial oxadiazole (13).



Scheme 4 : Utilization of some acetic acid derivatives for the synthesis of lead antifungal (17).

In the same context, reaction of ethylcyanoacetate with ortho diamine resulted in synthesis of compound **23** which was utilized as a starting material to give compound **24**. Compound **24** showed remarkable antifungal activity as well as Compound **25a** which exhibited potent antifungal activity with low MIC comparing with Cefoperazone and Fluconazole as reference drugs [25, 26]. It is worth to mention that the pyridoimidazole **25b,** as isostyer of **25**, was more active as a fungicide than **25a** and further research are under investigation. Compounds **26** were obtained via the imidazole moiety active nitrogen nucleophilic addition to the isothiocyante molecules with subsequent ring closure involving the cyano group [25].

On the other hand, fatty acids are renewable resources that can be obtained from oleo biomass. Some of these acids were converted to their esters to participate in the synthesis of new series of biological active compounds **29**. The antifungal activity of them was screened and some of the newly synthesized compounds showed a broad spectrum of activity. The (SAR) studies demonstrate that the fatty chain in the synthesized compounds plays a crucial role in their biological activities. The increase in the number of carbon atoms of the side chain decreases the antimicrobial activity [26].

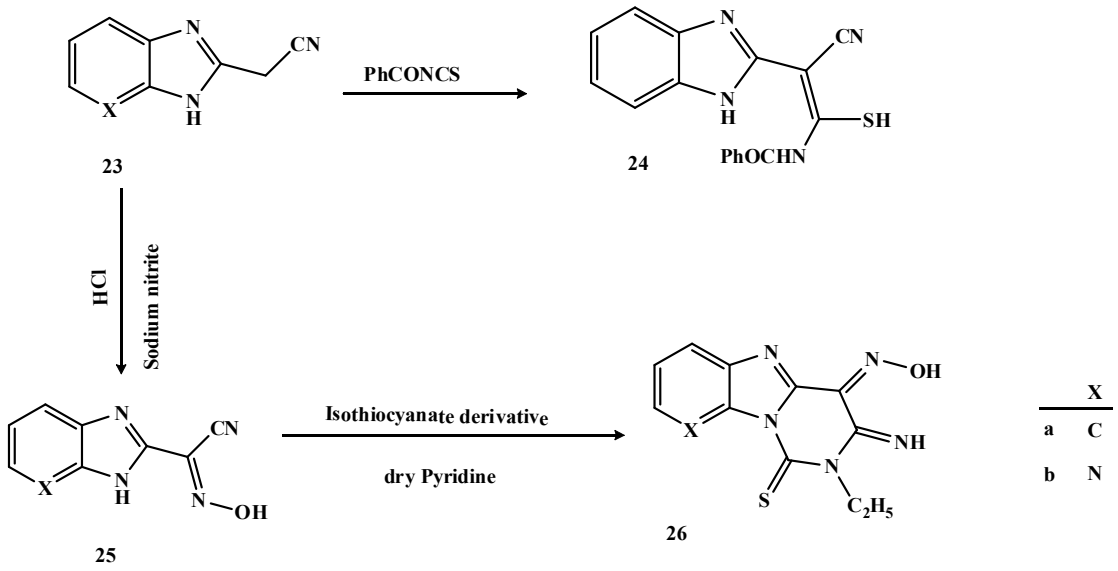


Scheme 5: Synthesis of lead fungicide 22.

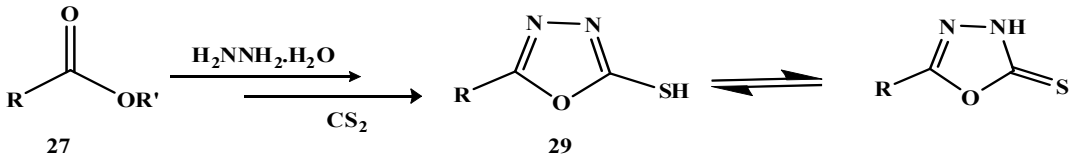
Pyrogallol, obtained from biomass driven gallic acid, was converted to pyrogallol actophenone to synthesize new series of pyrazolesincorporating 1,3,4 oxadiazole moiety. It has been synthesized utilizing our recently reported 4-formyl pyrazole which prepared from **2** via Vilsmeier reaction. A solution of compound **2**, ethanoli cNaOH and hydrogen peroxide was refluxed to afford **4** that gave compound **30** when heated under reflux with conc. H_2SO4in absolute ethanol or with thionyl chloride in benzene. By the reaction of **30** with hydrazine hydrate followed by the addition of carbon disulfide and potassium hydroxide, compound **32** was synthesized and it was found to be the highly active fungicidal agent in this series [14].

Lead Antiviral molecules obtained via same mentioned approach

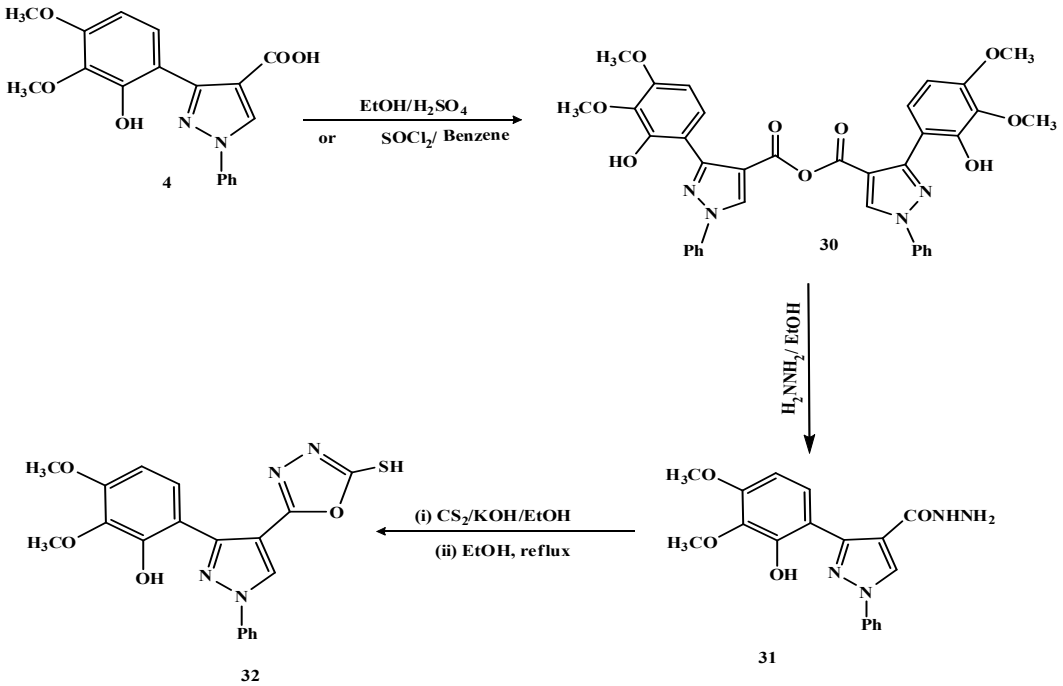
Viral diseases are extremely widespread infections. Some familiar viral diseases include common cold, influenza, chickenpox, herpes, gastroenteritis (stomach flu), human immunodeficiency virus (HIV/AIDS), and hepatitis. They can lead to serious, and potentially life-threatening complications, it was estimated that viral infections are responsible for more than 60% of the illnesses occurring in developed countries. Antivirals are compounds used since the 1960s that can interfere with viral development. It was estimated that viral infections are responsible for more than 60% of the illnesses occurring in developed countries [27]. Antivirals display



Scheme 6: New antifungal, analgesic and antiinflammatiry agents utilizing acetic acid derivative.



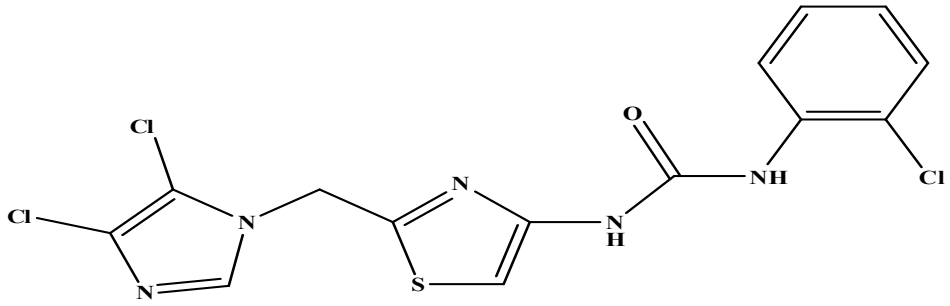
Scheme 7: Utilization of fatty acids in the synthesis of new series of antifungal compounds.



Scheme 8: Lead antifungal utilizing Pyrogallol.

various mechanisms of action, and while some of them enhance the animal immune system, others block a specific enzyme or a particular step in the viral replication cycle. Antiviral drugs play an important role in fast-spreading epidemics; however almost all antivirals are subjects to drug resistance as the pathogens mutate over time, becoming less susceptible to the treatment. In addition, the most important condition that must be possessed as an antiviral drug is to inhibit the virus in the cell and have no effect on the normal metabolism of cell. At present, a large number of antiviral drugs have serious side effects, which makes it difficult to develop effective antiviral agents with little side effects [28]. Therefore, there remain important medical needs to improve upon the current therapy as well as those there exists no treatment [27].

In this context, West Nile Virus (WNV), a human pathogen rapidly expanding worldwide, is a member of *Flaviviruses*, a genus that infects millions of people worldwide and is the cause of tens of thousands of fatalities annually [29]. Infection in humans is generally asymptomatic or causes a mild febrile disease in about 20-30% of cases. The most severe cases of WNV infection result in encephalitis or meningitis. Around 10% of cases of neuroinvasive disease are fatal and the survivors may suffer from long-term cognitive and neurological impairment [30]. Unfortunately, there is no effective human vaccine or effective antiviral therapy available for WNV.



33

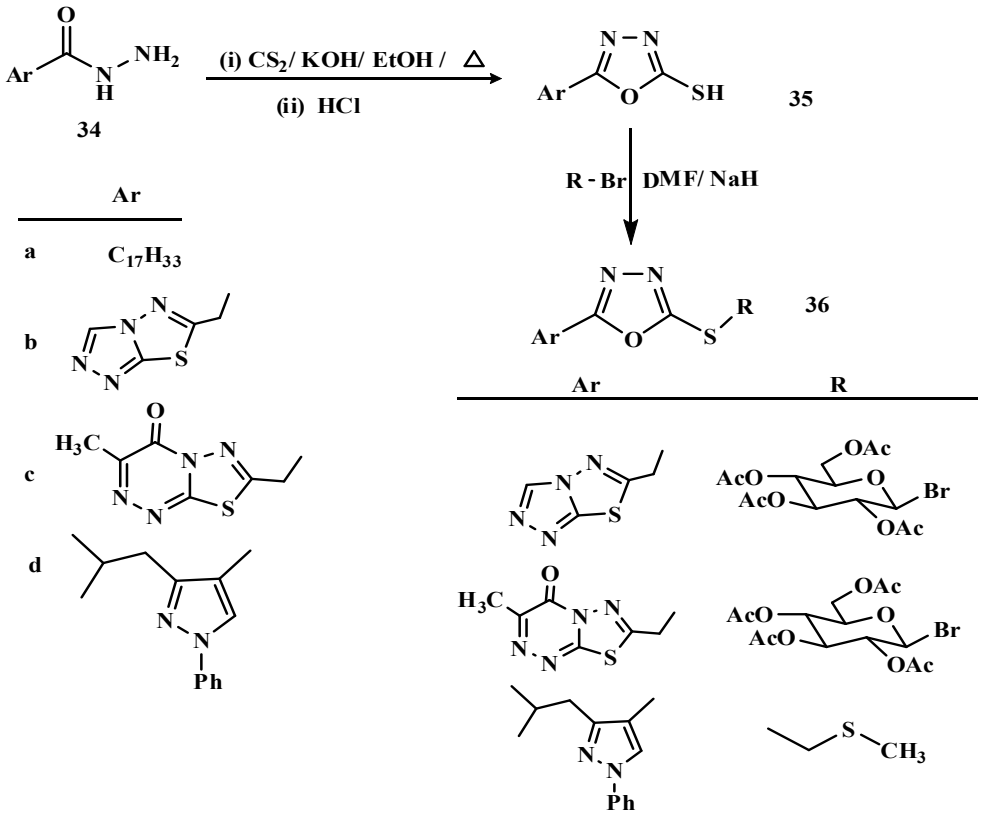
Scheme 9: Potent antiviral incorporating urea moiety.

Among the continued medicinal chemistry efforts done, Paul R. Young et al. [31]. reported the *in silico* screening of small molecule libraries using the dengue virus envelope E protein to identify compounds with antiviral activity against multiple flaviviruses. The biological evaluation of the most promising compounds obtained from the computer-based simulation revealed that compound **33** containing the urea moiety, has antiviral activity against both WNV and yellow fever virus. Comparing to other studied compounds, it was suggested that that linkage of thiazole ring via urea/hydrazone to a large aromatic group is the key components for antiviral activity [32].

Obtained potent antitumor compounds utilizing biomass building blocks

Cancer is one of the most dangerous diseases that threaten humanity. Although several drugs are used with different structures and mechanisms of antitumor activities, they failed to defeat cancer completely due to the development of drug resistance, side effects and failure of anti-tumor drugs to exert their effects in certain cases of cancer. Therefore, seeking for new chemotherapeutic agents via synthetic or natural origins is one of the most topics of concern to the scientific researchers.

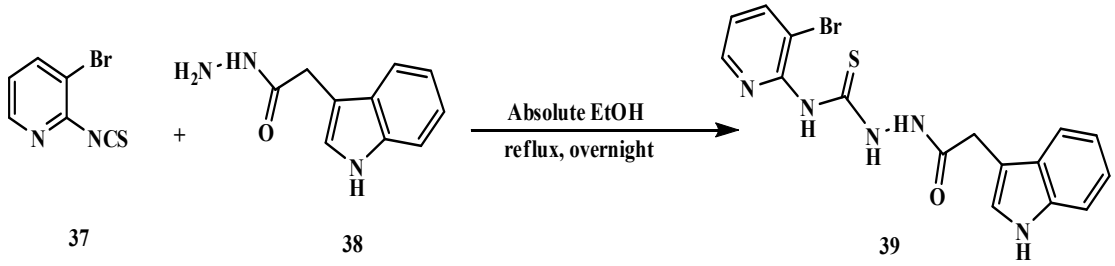
Among the great efforts done, a new series of thioglygosideoxadiazole **35** derivatives was synthesized. Compounds **35** and **36** showed potent antitumor activity when tested against different cell lines [26,33,34]. The (SAR) studies for compound **35a** with other fatty derivatives demonstrate that the fatty chain in the synthesized compounds plays a crucial role in their biological activities. The increase in the number of carbon atoms of the side chain increases the antitumor activity. The molecular Docking study showed that the activity of compound **35a** is due to its good interaction with amino acids and it exhibited good fitting in the binding sites [26].



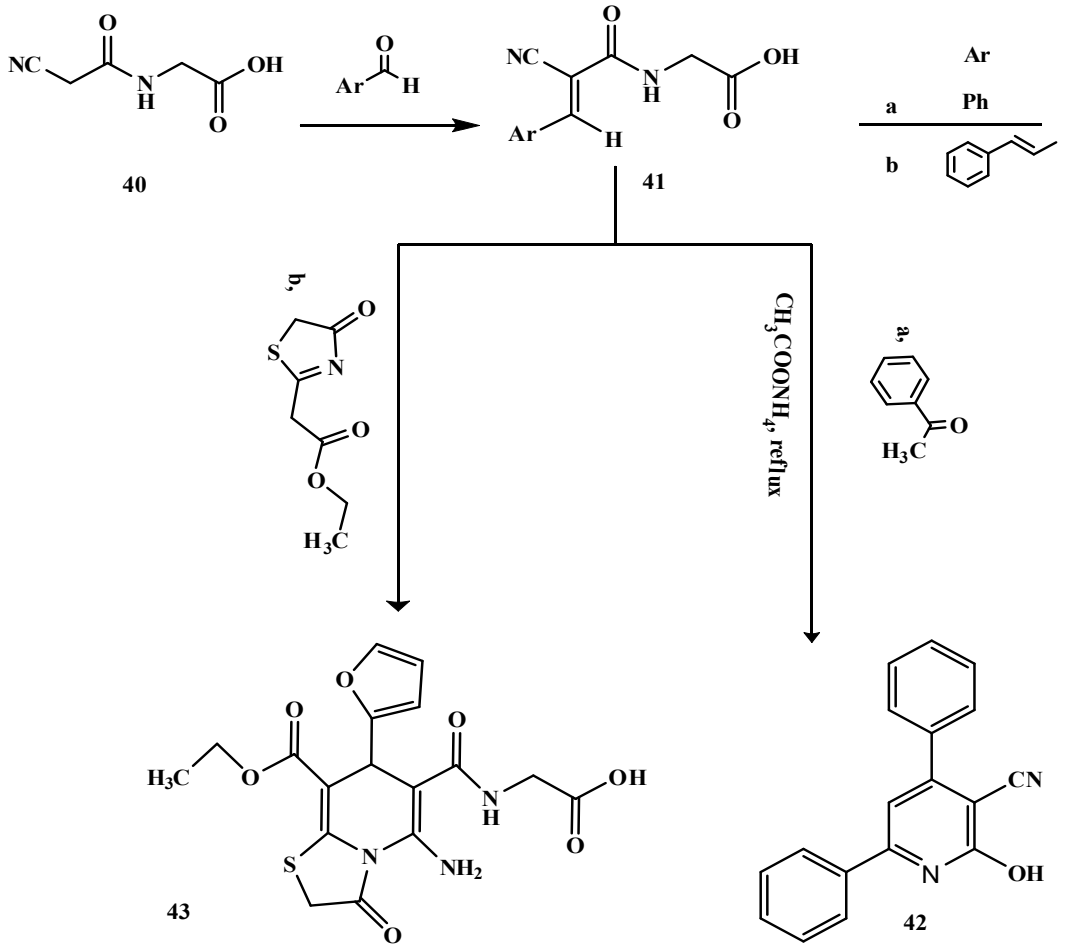
Scheme 10: New series of thioglycoside oxadiazole derivatives as potent antitumor agents.

In continuation to our work, we reported the identification of a series of compounds with anticancer activity by a combined virtual screening approach on the kinase domains of HER1 and HER2 which are considered important targets in anticancer therapy with dual HER1/ HER2 inhibitor. The newly synthesized 1,4 disubistitutedthiosemicarbazide **39**, obtained from naturally occurring 3-indole acetic acid, exhibited high antitumor activity. In addition, The ELIS Assay suggested that compound **39** could target HER1 and HER2 kinase domains and represent a good starting point for the development of novel anticancer compounds. However, further studies will be needed to confirm the mode of action of this compound [35].

Because of the high reactivity of 3-oxoalkanocarboxylates as polyfunctional compounds, we directed our work utilizing some of them to synthesize new heterocyclic compounds. Acetylated glycine, for example, was utilized via a simple route for the synthesis of various heterocyclic compounds [36-38]. Following this route, reaction of cyanoacetyl glycine **40** with different aldehydes resulted in the synthesis of new series of ylidines which are active precursors for the new compounds **42** and **43** that exhibit potent antitumor activity [14].



Scheme 11: Lead antitumor agent utilizing indole incorporating ureayl residue.



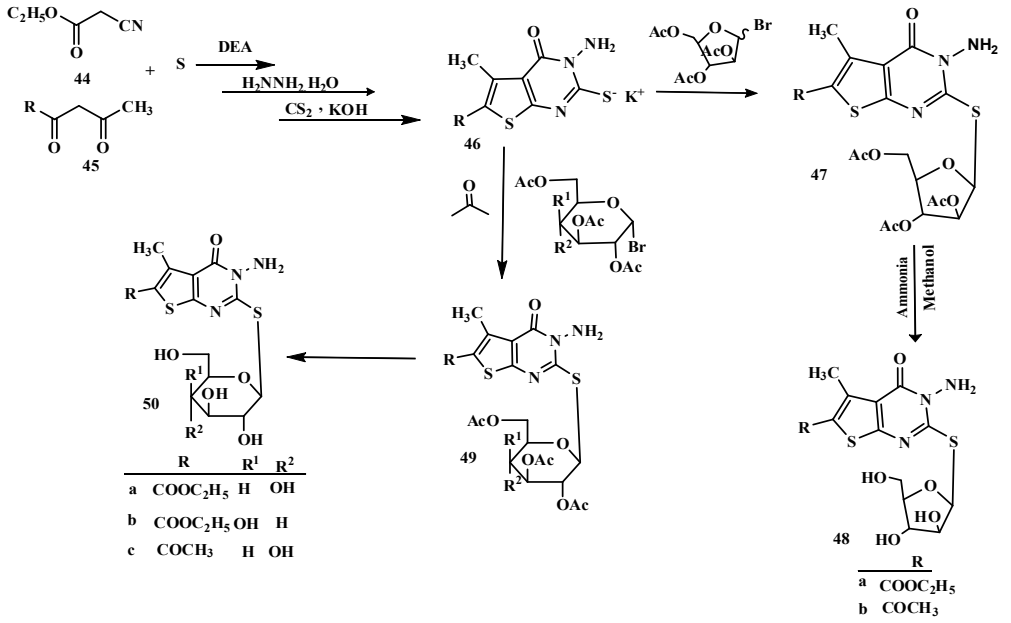
Scheme 12: Synthesis of lead antitumors 42 and 43.

Analgesic and Anti-inflammatory obtained leads

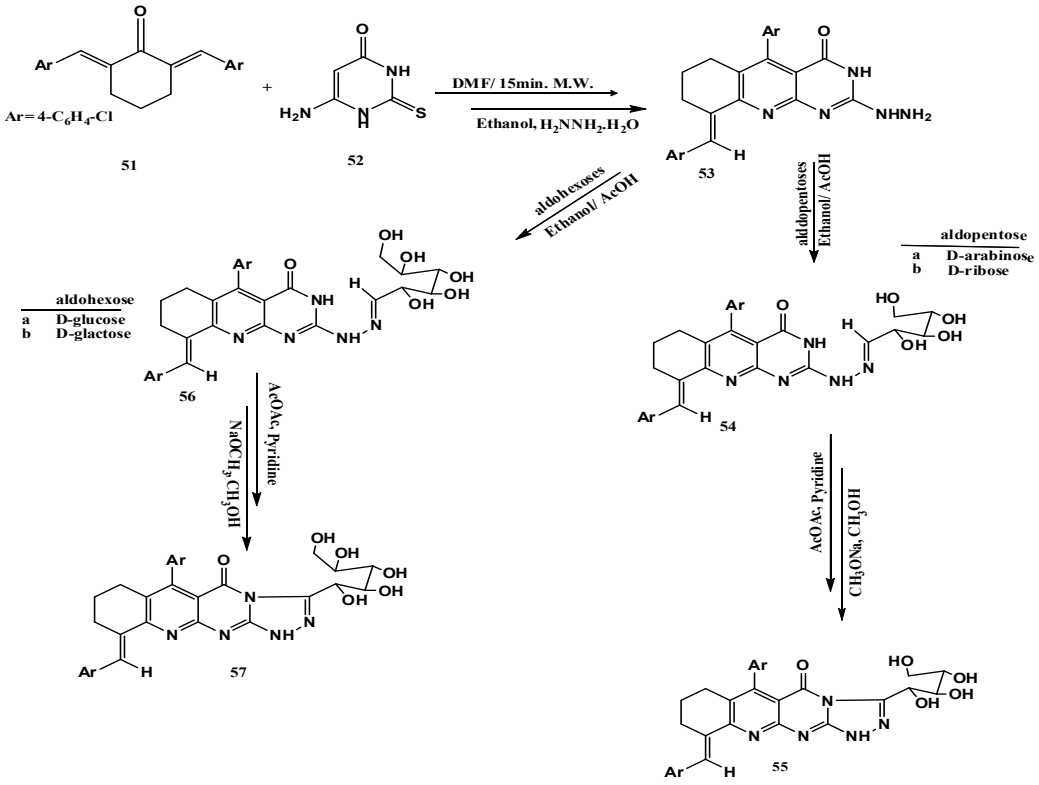
Recently, pyrimidines derivatives have generated great interest due to their wide spectrum biological activity. There is a large number of pyrimidine-based antimetabolites. They are usually structurally related to endogenous substrates they antagonize. The structure modification may be on the pyrimidine ring or on the pendant sugar groups. In the hope of finding more effective analgesic and anti-inflammatory drugs, we directed our attention to synthesize new derivatives of *S*-glycosido-thieno[2,3-*d*] pyrimidine. Among the compounds examined in our study, were compounds **48a,b** and **50a-c** which possess the most prominent and consistent activity. It was clear that compounds bearing 2-(b-D-ribofuranosylthio)residues **48a,b** displayed the best activity. By contrast, 2-(b-D-galactopyranosyl-thio)-**50a-c** analogs were less active. It can be hypothesized that the larger substituent causes decrease in the activity for this series and may be detrimental to the overall activity. Among the compounds, it was appeared that presence of an ethyl carboxylate substituent in position-6 of the 3-aminothieno[2,3-*d*] pyrimidine nucleus led to more active compounds (**48a** and **50a,b**) compared with acetyl substituted derivatives in the same position of 3-aminothieno[2,3-d]pyrimidine (**48b** and **49c**) [39].

In continuation to elucidate effective analgesic and anti-inflammatory therapeutics, we started our work utilizing precursors with pyrimidine moiety. Heterocycles bearing a symmetrical pyrimidoquinoline moiety are reported to show a broad spectrum of pharmacological and medicinal properties including analgesic and anti-inflammatory activities. In addition,

Microtechnology has attracted much interest for the rapid synthesis of organic compounds which are not easily accessible by conventional synthetic techniques. Therefore, we applied Microwave techniques to synthesize the starting material of our new (2-thioxy-pyrimido[4,5-*b*]quinoline) derivatives. Compounds **55a,b** and **57a,b** showed more potent anti-inflammatory and analgesic activities [40].



Scheme 13: Synthetic route for *S*-glycosido-thieno[2,3-d] pyrimidine as potent analgesic and antiinflammatory .

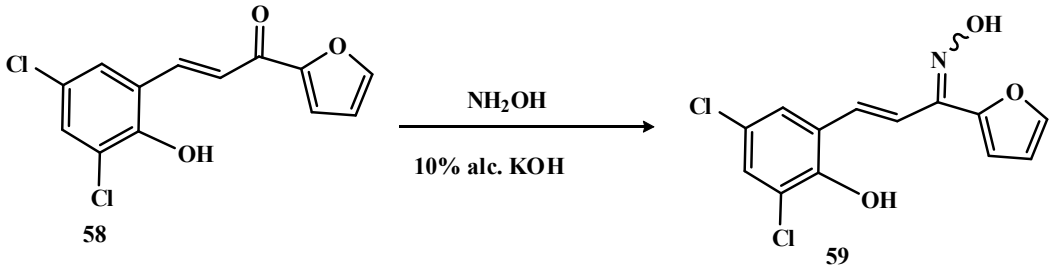


Scheme 14: 2-thioxy-pyrimido[4,5-b]quinoline derivatives as lead antiinflammatory and analgesic .

In addition, new benzimidazole and imidzopyridine derivatives were designed and synthesized from their corresponding oximes **25**. The newly synthesized compounds were investigated in *vivo* for their anti-inflammatory and analgesic activities. Some of the new compounds **26c-e** showed reasonable anti-inflammatory and analgesic activity in experimental rats in comparing to indomethacin and Diclofenac Na, as reference drugs. Compounds **26c-e** were found to be potent anti-inflammatory and analgesic agents with percent Oedema inhibition (33.92%, 33.92% and 37.63%). And protection percent as analgesic agents (68.84,75.04% and 77.04%) respectively. In particular, compound **26e** showed the most potent anti-inflammatory and analgesic activity. Moreover, docking studies of compounds that have highest anti-inflammatory activity showed that compound **26e** displayed stronger binding interactions with the active site of the human COX-2 enzyme (cf. Scheme 6) [25].

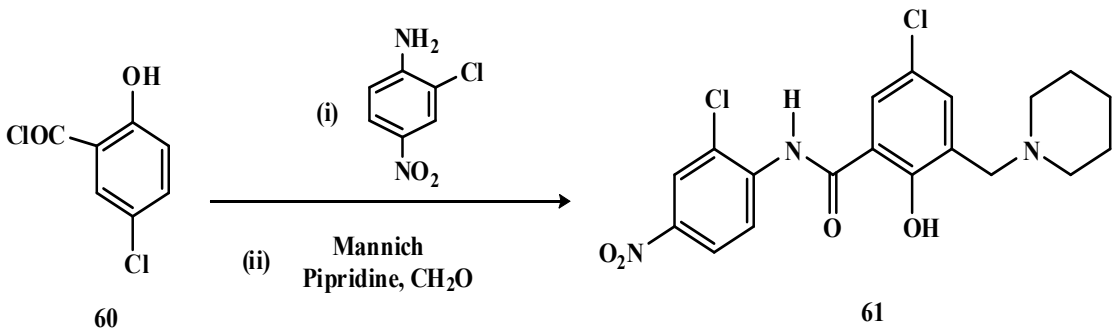
Discovered lead Molluscidial molecules

In continuation to our work aiming to develop new heterocyclic systems with expected biological potentialities from biomass driven starting materials, we were seeking for new compounds with molluscisidal activity in a trial to solve many health problems in our country. 1-(2-hydroxy/substituted phenyl)-3-(2-furyl) propenone **58**was tested as moluscicidal agent and it showed the most promising result. In an attempt to improve its activity, new derivatives of it were synthesized. As oximes are known for their biological importance, the propenone **58** was treated with $H_2NOH.HCl$ in aqueous-methanolic KOH solution, affording compound **59** which exhibited most effective molluscicidal activity [41].



Scheme 15: Synthesis of new derivatives of 1-(2-hydroxy/substituted phenyl)-3-(2-furyl) propenone with molluscicidal activity.

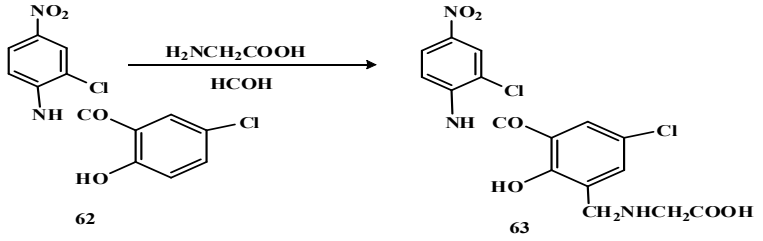
As it's known that salicylanilides represent an important class of molluscicides, we reported the treatment of5-chloro-2-hydroxybenzoyl chloride**60** with piperidine and formaldehyde in a Mannich type reaction affording the corresponding 3-(N-piperidinomethyl)salicylanilides**61**. The toxicity of this product to *Biomphalaria Alexandria* snails was evaluated and the result showed that compound **61** is the most effective. [42]



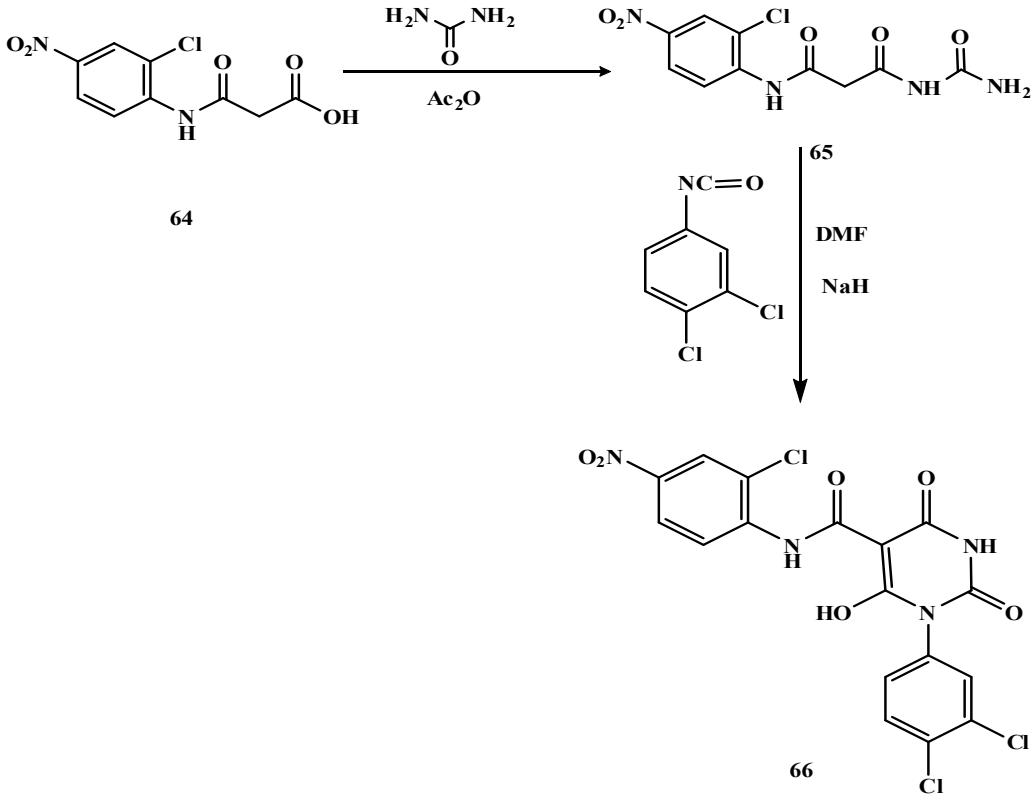
Scheme 16: Synthesis of the most effective molluscicidal 3-(*N*-piperidinomethyl)salicylanilides.

On the other hand, we constructed new salicyloyl amino acid conjugates utilizing Mannich reaction, as amino acid conjugations are known to improve the pharmacokinetics and toxicity of active drug. The toxicity of the productto*Biomphalariaalexandria* snails was evaluated and the result showed that the salicylanilide containing the *N*-glycinomoiety **63** has the same Molluscicidal activity as the known mollusicide Pilocid but without the disadvantage of Pilocid a raised from its bad water solubility [43].

The structure activity relationship studies showed that the acidity of salicylanilide moiety is an important feature in its molluscicidal activity. Accordingly, the 3-nitro derivatives were chosen as starting compounds for the synthesis of new salicylanilides. Water solubility and biodegradability were considered as disadvantages in the Pilocidmolluscicide. Pyrimidosalicylanilide **66** with potent molluscicidal activity was designed and synthesized as a heterocyclic analogue hoping to overcome these disadvantages. It was synthesized starting with malonic acid derivative **64**, followed by acylating urea to give **65**. To a solution of compound **65** in DMF, NaH was added followed by the addition of 3,4-dichlorophenyl isocyanate to afford compound **66** which showed promising molluscicidal activity [44].



Scheme 17: Better slouble pilocid® derivative.

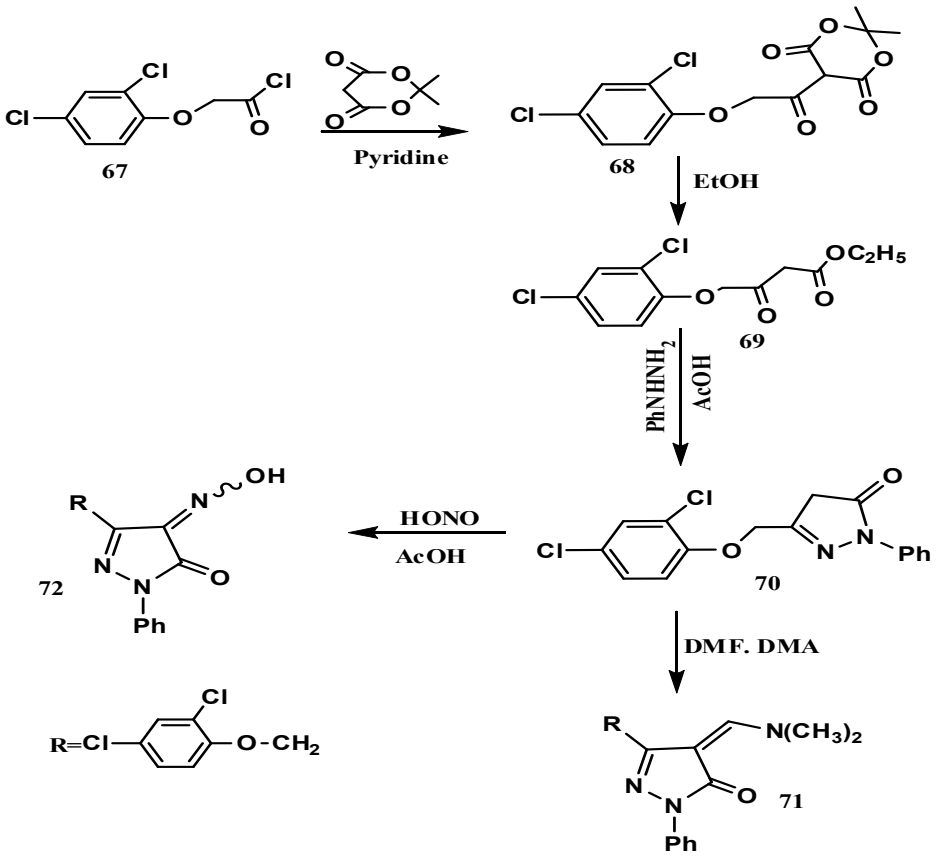


Scheme 18: Heterosalicylanilide analouge as lead molluscicide.

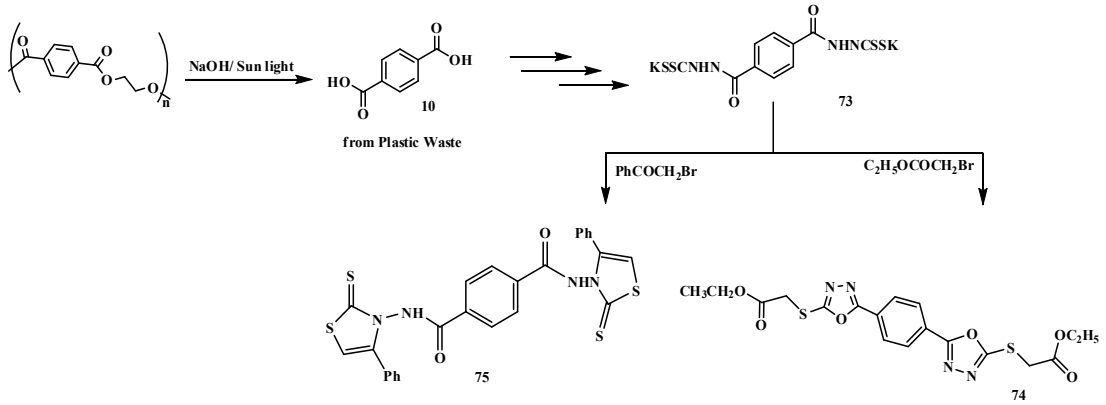
The idea of preparing new azoles carrying the 2,4-dichlorophenoxy moiety which has herbicidal activity seemed to be interesting. Therefore, hoping to obtain compounds that combat snails and water hyacinth shelter in the same time. Compounds **70**, **71** and **72** showed most promising Molluscicidal activity [45].

Lead Insecticidal molecules via the same above mentioned approach

Recycling of solid waste (PET) using sunlight to afford new bis (1,3,4-oxadiazole) **74** and1,3-thiazolidine derivatives **75** via utilizing (PET) monomer terephthalic acid which esterified and treated with hydrazine hydrate to afford the corresponding hydrazide that coupled with carbon disulphide to give adduct **73**. Interestingly, these compounds **74** and **75** exhibited good *in-vitro* insecticidal activity against the *Cluexpipiens* and *Muscadomestica* [46].

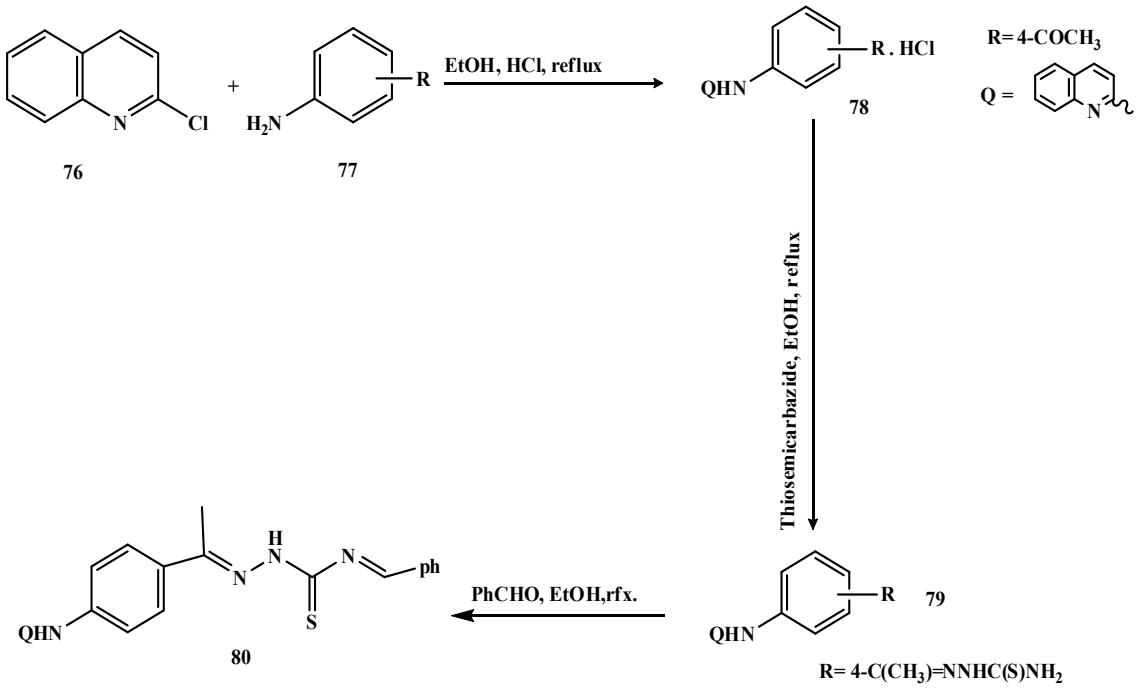


Scheme 19: Design and sythesis of potent molluscicides having herbicidal activity.



Scheme 20: Valorization of PET wasteand produce potant insecticiads.

Besides, a series of quinolone derivatives have been elaborated and showed Anti Aphid *Aphis gossypii* that harm cotton crop in Egypt. Compound **80** was found to be more active than Marshal (Carbosulfan), one of the broad insecticides widely used in this field. It was synthesized by the nucleophilic substitution of 2-chloroquinoline **76** with the appropriate acetylaniline derivative **77** in refluxing EtOH containing drops of HCl to afford compound **78**. Thus, compound **78** was heated under reflux with thiosemicarbazide to give compound **79** which when heated under reflux in benzene and ethanol, the desired compound **80**was obtained [47].

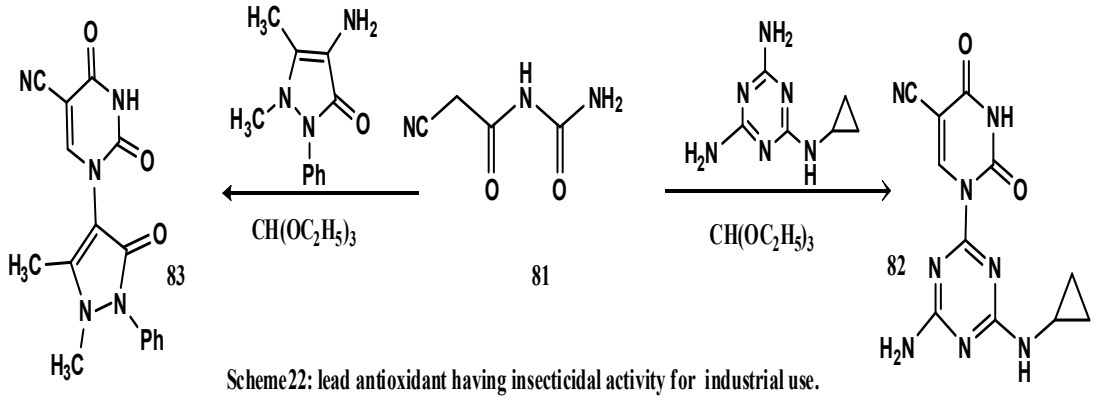


Scheme 21: Lead Anti Aphid.

Obtained lead Antioxidants

An antioxidant is a molecule that inhibits the oxidation of other molecules which is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells. Antioxidants such as thiols or ascorbic acid (vitamin C) terminate these chain reactions.

One of the several efforts that have been done to obtain new antioxidants, is a study carried out on the new heterocyclic compounds **82** and **83** activities and proved their efficiency as antioxidants on styrene butadiene rubber (SBR) mixes [48].

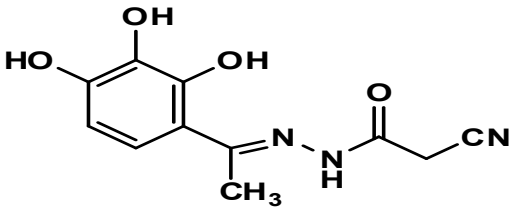


Scheme22: lead antioxidant having insecticidal activity for industrial use.

In the same context, the protective effects of the synthetic antioxidant "acetylgallate derivative" (SAC) **84** were investigated against hepatic oxidative stress and brain damage induced by dimethoate (DM) in male rats. The result showed that supplementation of SAC is more reliable than Vitamin C in attenuating relative liver weight, SOD, GST, and brain DNA damage [49].

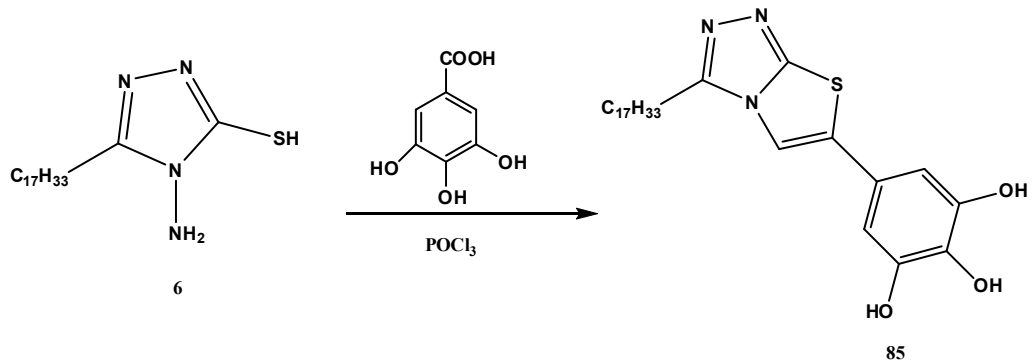
In addition, Compounds**11**and **12** (cf. Scheme 3) resulted from the recycling /management of poly ethylene terephthalate(PET) waste exhibited good radical radical scavenging activity [50].

In the same context, fatty acids are derived from renewable raw materials and exhibit various biological activities. Several researchers are amalgamating these bioactive components with heterocyclic compounds to yield bioactive hybrid molecules with some desirable features. Heterocyclic fatty acid hybrid derivatives are a new class of heterocyclic compounds with a broad range of biological activities and significance in the field of medicinal chemistry. New series of 3-olyl-6-substituted[1,2,4] triazolo[3,4-b]thiadiazoles, 3-olyl-6-substituted [1,2,4]-triazolo[3,4-b]thiadiazines, and *S*- or *N*-substituted 3-mercapto-1,2,4-triazoles was synthesized starting with oleic acid. Among the different compounds synthesized, compound **85** which is an analogue to vitamin C (ascorbic acid) showed high antioxidant activity [15].



84

Scheme23: Potent antioxidant utilizing pyrogallol.



6 **85**

Schemec 24: Developing the antioxidant activity of gallic acid via incorporating heterocyclic moiety.

Conclusion

Our future sustainability creates a great challenge in sciences and technologies. The exploration of new fundamental chemical reactivates could potentially result in chemical tools that are more efficient in resource and energy utilization with less accumulation of waste. The examples presented in this review illustrate our efforts toward the low-cost discovery via chemical synthesis with an eye on future sustainability. Simple synthetic routes and processes utilizing waste driven building blocks could present a low cost strategy for inventing novel solution for different chronic health, agricultural and industrial problems in Africa and other developing countries. Cooperation between developed country and African countries for example will allow quick application of the newborn low cost discoveries. The waste-based bio-economy is an important component of the transition from a linear – take, make, dispose – economy to a sustainable circular economy.

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"تتلة الحيوية"المشاركة عبر الابتكارات قليلة التكلفة في المجهودات العالمية لمكافحة الامراض: طرق كميائيه بسيطة للمركبات الفعالة باستخدام وحدات بنائية من الكتلة الحيوية

جلال عبد المعين محمود نوار, رنده حلمي سويلم ,هدى صبري عثمان أحمد
قسم الكيمياء الخضراء - المركز القومي للبحوث - الجيزة -مصر.

من بين مختلف الجهود العالمية المبذولة لاكتشاف أدوية, مواد حافظة و مبيدات آفات, ثمّة طرق تشييدية بسيطة وقليلة التكلفة بوسائل إنتاجية لتشييد مركبات ذات فاعلية بيولوجية عالية, وذلك عن طريق الاستفادة من مركبات أولية مستخلصة من الكتلة الحيوية.

هذا النهج الصديق للبيئة يناسب أيضا الباحثين المتواجدين حيث نقص التمويل و إمكانيات البحث .

كما أنه امكن استخدام مواد أولية متعددة النشاط, مثل: ٣-أوكسو ألكان كربوكسيلات, النيتريلات النشطة, وألفا-بيتا كيتونات غير المشبعة, لتشييد سهل لمختلف المركبات الصغيرة ذات الأهمية البيولوجية.

ونحن نلقي الضوء _من خلال هذا الاستعراض_ على بعض نماذج النتائج التشييدية لعدد من المركبات النشطة بيولوجيا, والتي نتجت خلال توجهاتنا المستمرة نحو هذا النهج.

وسوف يؤدي مزيد التطور من قبل الصناعة والأوساط الأكاديمية إلى إنتاج مكونات جديدة نشطة لمواجهة التحديات البيولوجية الخطيرة ومقاومة الميكروبات والحشرات.

خارج عن نطاق هذا الاستعراض ما قد حققه عدد من الباحثين من الانجازات العظيمة في كل من هذه الموضوعات.