Journal of the Iranian Chemical Society (2022) 19:23–54
https://doi.org/10.1007/s13738-021-02293-x

REVIEW

Recent investigation on heterocycles with one nitrogen [piperidine, pyridine and quinoline], two nitrogen [1,3,4-thiadiazole and pyrazole] and three nitrogen [1,2,4-triazole]: a review

Zabiulla[1] · Fares Hezam Al-Ostoot[2,3] · Asha M. S[1] · Mohammed Al-Ghorbani[4] · Shaukath Ara Khanum[3]

Received: 8 February 2021 / Accepted: 21 May 2021 / Published online: 21 June 2021
© Iranian Chemical Society 2021

Abstract
Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially, and about one half of over six million compounds recorded in chemical abstracts are heterocyclic. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. In the present work, focus on the literature survey of chemical diversity (piperidine 1, pyridine 2, quinoline 3, [1,3,4]-thiadiazole 4, pyrazole 5 and [1,2,4]-triazole 6) in the molecular framework in order to get a complete information regarding pharmacologically interesting compounds of widely different composition.

Keywords Heterocycles · Piperidine · Pyridine · Quinoline · [1,3,4]-thiadiazole · Pyrazole · [1,2,4]-triazole

Introduction

The synthetic chemistry can rightfully be considered a precondition of our modern society [1]. This discipline benefits many valuable resources to our world, enabling us to produce the quantities of fertilizer needed to feed a growing world's population and produce the numerous customized materials without which society could not progress. Apparently, synthetic chemistry has an enormous influence on community health where treatments for almost any disease can be established resulting in a steady increase in life expectancy [2, 3]. All these advances have been enabled by the interest of generations of scientists constantly searching for new solutions to the assembly of functional molecules. Significantly, this has required the growth of many new methods for selectively forming new chemical bonds, allowing the generation of more complex drugs [3, 4]. Nevertheless, one downside of drug research lies in the enormous cost of the development and regulatory processing of a new drug with only 15–20 years of commercial protection being granted to recoup this initial outlay [3, 5]. As a result, pharmaceutical companies are continuously seeking ways to accelerate this development process by adopting new synthetic procedures and enabling technologies in order to profitably generate new medications for both old and new targets [6]. By studying the synthetic routes used to construct modern pharmaceutical structures, a general overview of the most valuable synthetic

✉ Shaukath Ara Khanum
shaukathara@yahoo.co.in

[1] PG Department of Studies and Research Centre in Chemistry (A recognized research centre of University of Mysore), St. Philomena's College Bannimantap, Mysuru, Karnataka, India

[2] Department of Biochemistry, Faculty of Education and Science, Al-Baydha University, Al-Baydha, Yemen

[3] Department of Chemistry, Yuvaraja's College (Autonomous), University of Mysore, Mysore, Karnataka, India

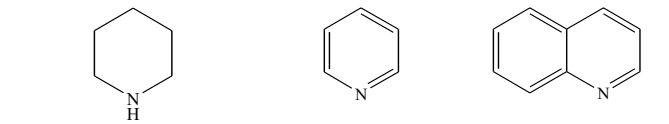
[4] Department of Chemistry, Faculty of Science, Thamar University, Thamar, Yemen

techniques and best working practices as used by the pharmaceutical industry can be created [3]. The contribution of medicinal organic chemistry to the biological, medicinal and pharmaceutical field is vast, including drug development, detection, design and identification of bioactive compounds.

An introduction to heterocyclic compounds

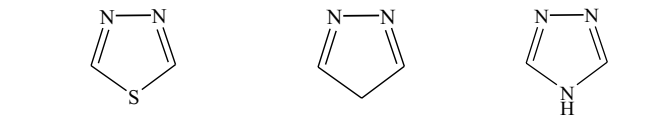
Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In detail, two-thirds of organic compounds are heterocyclic compounds. A cyclic organic compound comprising all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon forms a part of the ring system, then it is referred as a heterocyclic compound [7, 8].

Heterocyclic compounds represent dynamic important role in medicinal chemistry and have paying healthy interest with a broader scope to synthesize and process numerous types of pharmacological properties. Besides the enormous distribution of heterocyclic compounds in natural products, they are also the major components of biological molecules such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Indeed, DNA is without doubt the most important macromolecule of life and the monomer of RNA and DNA, i.e., nucleotides, the building blocks of our genes are derivatives of purine and pyrimidine bases. Chlorophyll, a green color pigment helps in the synthesis of oxygen by absorbing carbon dioxide in plants and heme, the non-protein part of hemoglobin is the oxygen carriers in animals that are derivatives of large porphyrin rings. However, synthetic heterocyclic compounds have extensive therapeutic uses available in many therapeutic categories such as antibacterial [9], antifungal [10], analgesic [11], anti-inflammatory [12], antimycobacterial [13], antitubercular [14], antimalarial [15], trypanocidal [16], anti-HIV activity [17], anticonvulsant [18], antitumoural [19], antileishmanial agents [20], genotoxic [21], herbicidal [22], anticancer [23] and lipid peroxidation inhibitors [24], hypnotics [25], antidepressant [26], anthelmintic [27] and insecticidal agents [28]. Also, they have been widely found as a key structural material in synthetic pharmaceuticals and agro-based chemicals. Most of the heterocyclic compounds possess important applications in material science, such as fluorescent sensor and dyestuff, brightening agents, plastics, information storage and analytical reagents [29]. In addition, many of the heterocyclic compounds can also be used in making organic conductors, semiconductors, photovoltaic cells, molecular wires and organic light-emitting diodes (LED), light harvesting systems, optical data carriers, chemically controllable switches and liquid crystalline compounds [30–32]. Heterocyclic compounds are also of considerable interest because of their synthetic utility as synthetic intermediates, chiral auxiliaries, protecting groups and metal ligands in asymmetric catalysts in organic synthesis [33, 34]. By looking at the enormous applicability cross the spectrum of utilit, a greater amount of attention has been drawn to develop efficient new methods to synthesize heterocyclic compounds. Encouraged by the above literature information, this paper comprises of synthesis, characterization and pharmacological application of piperidine 1, pyridine 2, quinoline 3, [1,3,4]-thiadiazole 4, pyrazole 5 and [1,2,4]-triazole 6 derivatives.



Piperidine **Pyridine** **Quinoline**

1 **2** **3**



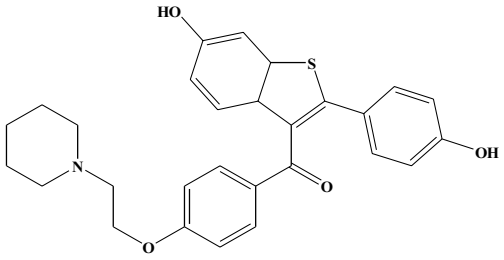
[1,3,4]-Thiadiazole **Pyrazole** **[1,2,4]-Triazole**

4 **5** **6**

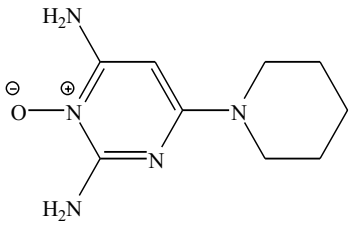
Introduction and synthesis of piperidine and its derivatives

Piperidine 1 or, azacyclohexane, is a common structural unit in natural products. Piperidine 1 is an organic compound with the molecular formula $(CH_2)_5NH$. This heterocyclic amine consists of one NH unit and five methylene units in six-membered ring. The piperidine moiety is an attractive drug template because of its useful pharmacological applications as antimicrobial [35], antitubercular [36], anti-inflammatory [37], herbicidal [38], insecticidal [39], fungicidal [40], bactericidal [41], antihistaminic [42] and central nervous system (CNS) stimulant [43]. Thus, piperidine nucleus containing molecules plays a very important role in the field of medicinal chemistry.

Besides, several hundreds of piperidine derivatives have been studied in both clinical and preclinical trails [44]. Nevertheless, the variety of substitution and functionality patterns are found in piperidine compound targets and are extensively accepted. The biological properties of piperidines are highly dependent on the location and type of substituent on the heterocyclic ring [45]. Piperidine derivatives are found to possess many pharmacological activities and form an essential part of the molecular structure of important drugs such as raloxifene 7 and minoxidil 8 [46].



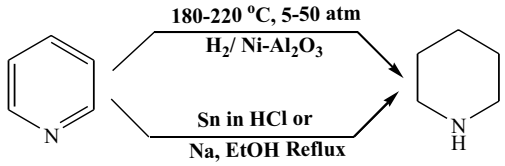
7



8

Interestingly, piperidine 1 can be easily prepared by reducing pyridine 2.

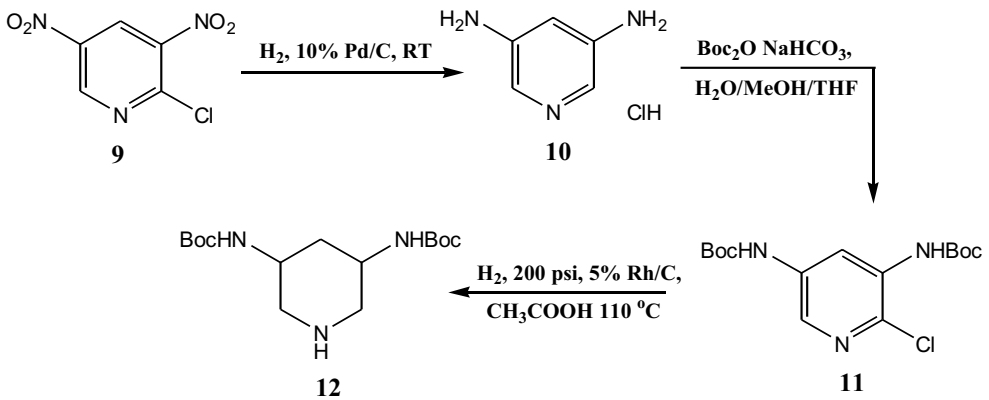
In this process, the reducing agents used are hydrogen and nickel, palladium or ruthenium catalysts at 180–220 °C and also using tin in hydrochloric acid or sodium in ethanol (Scheme 1).



2 1

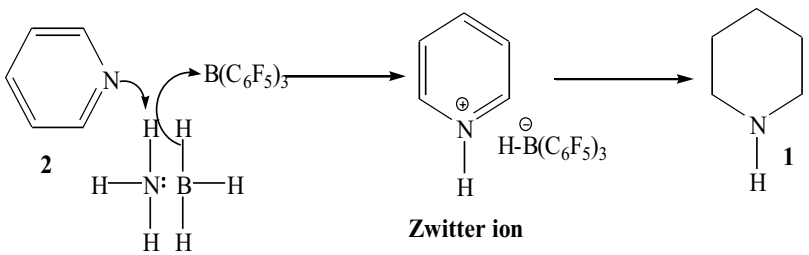
Alternatively, Zhou et al. prepared the 3, 5 tert-butyloxycarbonyl (Boc)-protected diamino piperidine 12 starting from hydrogenation of 2-chloro-3,5-dinitropyridine 9, which on reduction furnished 2-chloro-3,5-diaminopyridine 10, which undergo further hydrogenation after protection of amino group by Boc via an intermediate 11, at 2200 psi

Scheme 1 Synthesis of piperidine from pyridine

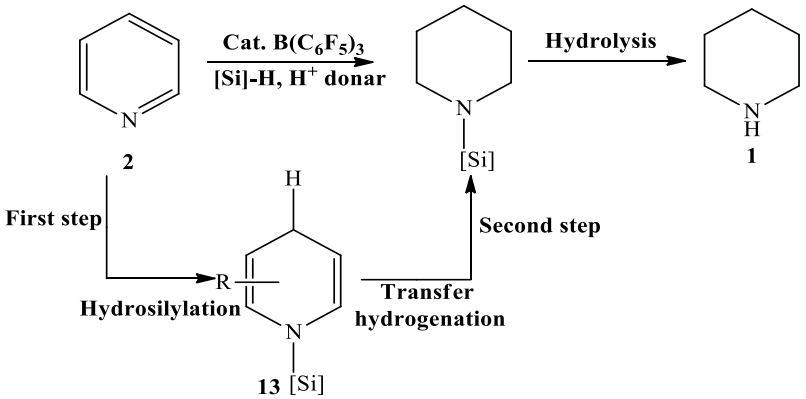


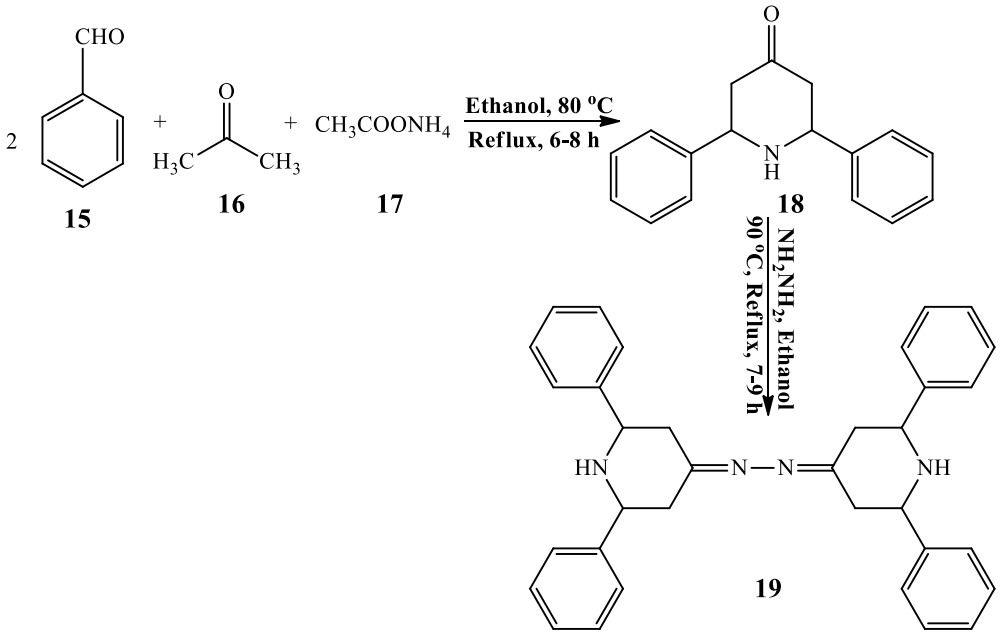
Scheme 2 Synthesis of piperidine from 2-chloro-3,5-dinitropyridine

Scheme 3 Synthesis of piperidine from pyridine using tris(pentafluorophenyl) borane



Scheme 4 Synthesis of piperidine from pyridine using $B(C_6F_5)_3$





Scheme 5 Synthesis of piperidine derivative from benzaldehyde and acetone

using 5% rhodium on carbon (Rh/C) as a catalyst in the presence of acetic acid at 110 °C as shown in Scheme 2 [47].

Further, Zhou et al. introduced an efficient and facile method for the hydrogenation of pyridine 2, using a borane catalyzed metal-free transfer with the use of ammonia borane as a hydrogen source which avoided use of high-pressure hydrogen.

They also proposed that the Lewis pairs are formed by pyridine and tris(pentafluorophenyl)borane $B(C_6F_5)_3$ which can split the B-H and N–H bonds of ammonia borane to form the Zwitter ionic species, which led to the subsequent reduction to form piperidine 1 as shown in Scheme 3 [48].

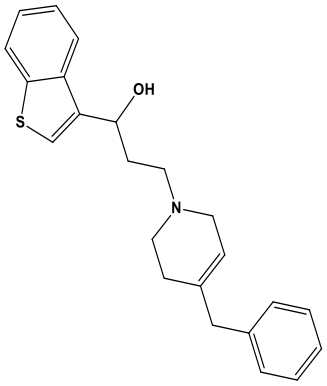
Recently, Wang et al. developed a $B(C_6F_5)_3$-catalyzed metal-free pyridine 2 reduction. The reaction was initiated by dearomative hydrosilylation to give the intermediate N-silyl 1,4-dihydropyridine 13, which further undergo rapid transfer hydrogenation and then, by hydrolysis to yield piperidine 1 (Scheme 4). This method features a broad functional group tolerance (e.g., ester, ketone, olefin, nitrile, nitro and heterocycles) and show more practical efficacy [49].

The synthesis of bispiperidine 19, by refluxing a mixture of benzaldehyde 15, acetone 16 and ammonium acetate 17 for 6–8 h was described by Singh et al. During this process, an intermediate 18 was generated, which on refluxing with hydrazine hydrate about 7–9 h at the temperature about 90 °C furnished compound 19 as depicted in Scheme 5 [50].

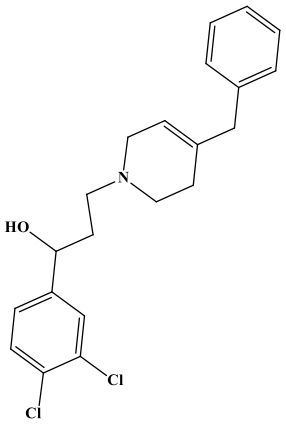
Pharmaceutical application of piperidine derivatives

Piperidine derivatives as antidepressant agent A series of arylalkanol-piperidine analogues were synthesized by Zheng et al. and evaluated for their triple reuptake inhibition and in vivo activities.

Among the series, compounds 20 and 21 showed a more significant reduction of immobility time compared to that of the vehicle in the mouse tail suspension test at doses ranging from 10 to 50 mg/kg po and were not generally motor stimulants at 50 mg/kg dose. Also, these compounds 20 and 21 displayed attractive pharmacokinetics activities in Sprague Dawley rats [51].

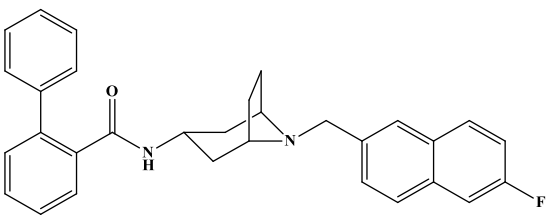


20



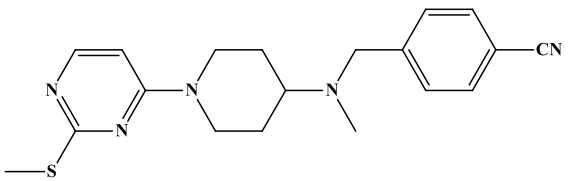
21

Piperidine derivatives as antiasthmatic agent A novel class of potent C–C chemokine receptor type 3 (CCR3) receptor antagonists was designed and synthesized with structural modifications by Sato et al. These compounds are a combination of the benzamide and piperidine moieties which led to the identification of *N*-{8-[(6-fluoro-2-naphthyl)methyl]-8-azabicyclo [3.2.1]oct-3-yl}biphenyl-2-carboxamide 22 as a potent CCR3 antagonist with an IC_{50} value of 0.020 μM [52].



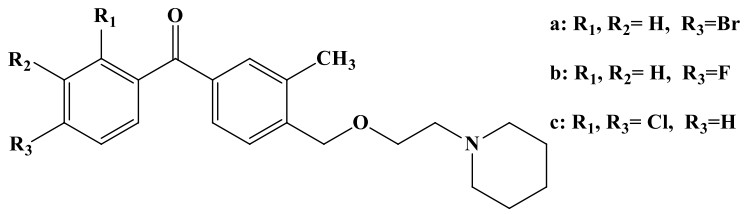
22

Piperidine derivatives as anticancer agent In the year 2015, Zeng et al. designed and synthesized piperidine derivatives as a novel human heat shock protein 70 (HSP70) inhibitors. The evaluation of biological activity reported that the synthetic compound 23 as HSP70 inhibitor has a good antitumour activity, especially in lapatinib-resistant cancer cells [53].



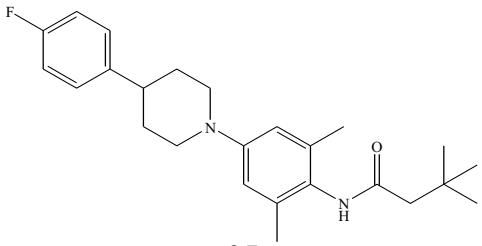
23

Piperidine derivatives as anti-inflammatory agent Khanum et al. prepared a sequence of benzophenone-*N*-ethyl piperidine ether analogues 24a-c and evaluated as orally active anti-inflammatory agents with reduced side effects. The anti-inflammatory and ulcerogenic activities of the compounds were compared with the standard compounds like naproxen, indomethacin and phenylbutazone [54].



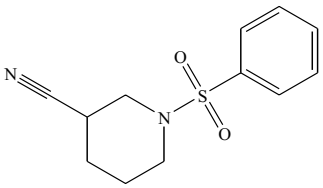
24a-c

Piperidine derivatives as antiepileptic agent Besides, Yang et al. have been designed and synthesized substituted piperidine derivatives targeting KCNQ (voltage-dependent potassium channel that is mostly associated with epilepsy) openers as novel antiepileptic agents. Moreover, they found that compound 25 have shown good pharmacokinetic profiles in vivo [55].



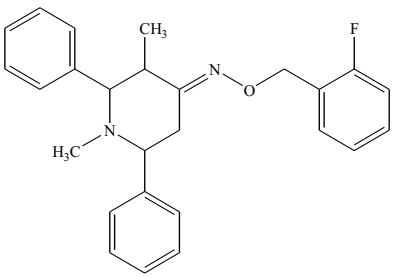
25

Piperidine derivatives as antidiabetic agent Type 2 diabetes (T2D) is a lifestyle disease affecting millions of people worldwide. Various therapies are available for the management of T2D and dipeptidyl peptidase-IV inhibition, which has emerged as a promising therapy for the treatment of T2D. Encouraged by this information researcher has reported the synthesis and in vitro efficacy of sulfonamide derivatives of pyrrolidine and piperidine as antidiabetic agents. Among all the synthesized series, compound 26 was found to be the most potent compound [56].

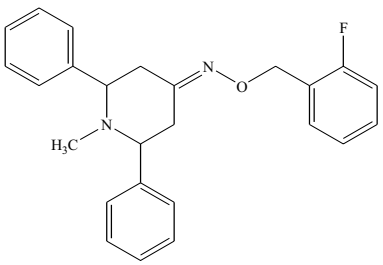


26

Piperidine derivatives as antimicrobial agent A series of piperidin-4-one oxime ether derivatives were synthesized and evaluated for antimicrobial activities. Among all the series, compound 27, exerted good inhibitory activity at a minimum inhibitory concentration (MIC) value of 64 and 128 μg ml^{-1} against *P. aeruginosa* and *S. faecalis*, respectively, and compounds 28, 29 and 30 exerted appreciable antibacterial activity at a MIC of 16–64 μg ml^{-1} against *S. faecalis*, *P. aeruginosa* and *S. aureus*.

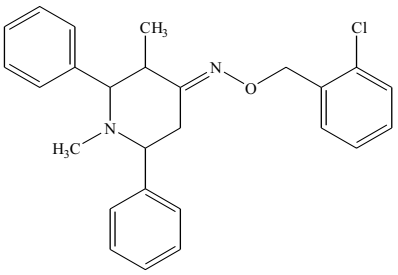


27

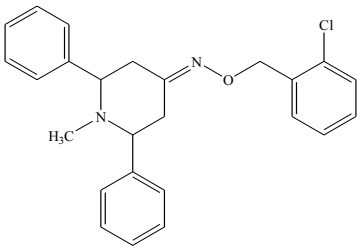


28

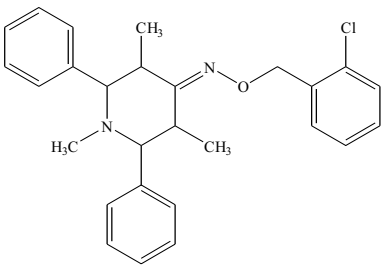
Whereas, compounds 29, 31 and 32 also showed good inhibitory activity against *A. flavus* [35].



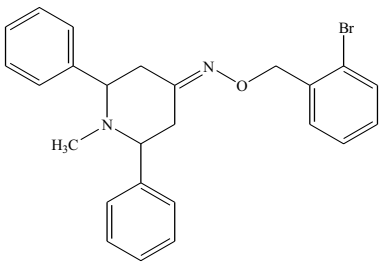
29



30



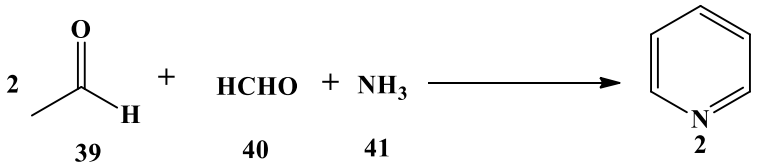
31



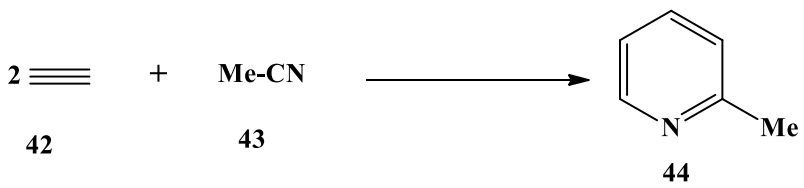
32

Piperidine derivatives as antitubercular agent Currently one quarter of the world's population is infected with tuberculosis and more than 95% of the death occurred in the developing countries. Based on these findings, Wardell et al. reported synthesis of antitubercular agents, in which diphenyl[((R,S)-2,8-bis(trifluoromethyl)quinolin-4-yl)-piperidin-2-yl-methanolato-O,N]boron 33 and (±)-erythro-mefloquinium tetraphenylborate 34 solvates (Mefloquine derivatives) crystalline solids exhibited antitubercular activity [57].

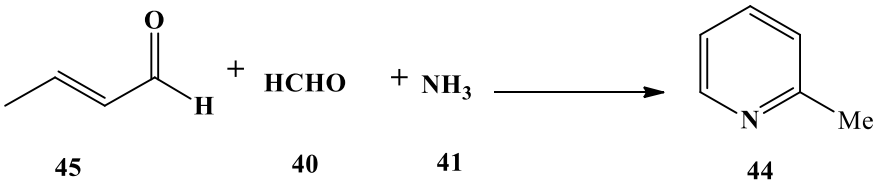
Scheme 6 Synthesis of pyridine using Chichibabin reaction

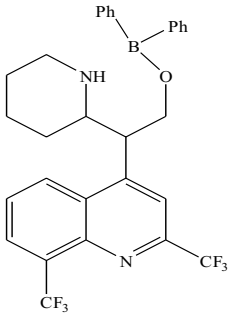


Scheme 7 Synthesis of pyridine from ethyne

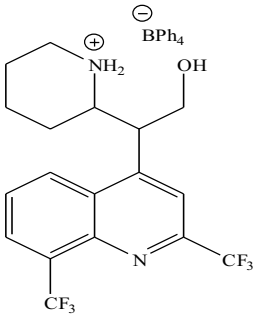


Scheme 8 Synthesis of pyridine from crotonaldehyde



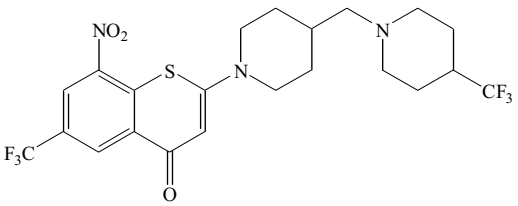


33



34

Furthermore, recently Kai et al. described the synthesis of benzothiazinones containing a piperidine moiety as a new antitubercular agents and found that among this series, compound 35 was found to display comparable in vitro antitubercular activity against drug-sensitive and resistant mycobacterium tuberculosis strains [58].

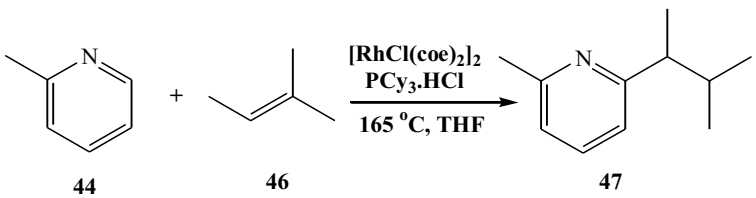


35

Introduction and synthesis of pyridine and its derivatives

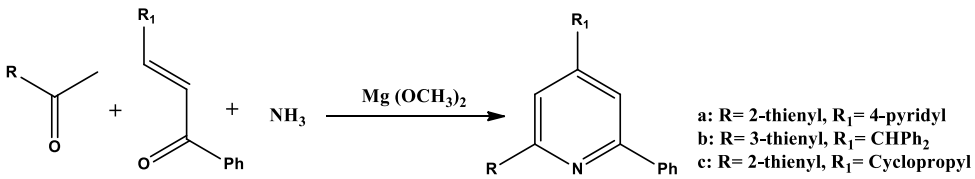
The synthesis of nitrogen heterocycles is an important area of research due to their prevalence in natural products and drugs [59]. In this class, pyridine 2 containing derivatives are the most extensively used in pharmaceutical research [60], and much effort has been devoted to their synthesis [61–63]. The pyridine ring can be considered as one of the simplest yet most important heteroaromatic structure. Naturally occurring many important compounds such as the vitamins niacin 36 (Vitamin B-3) and pyridoxine 37 (Vitamin B-6) are pyridine ring containing compounds. Further, niacin is required for the biosynthesis of the redox coenzyme nicotine adenine dinucleotide (NAD+), whereas pyridoxine is a coenzyme in transaminases and

Scheme 9 Synthesis of pyridine from2-methyl pyridine with 2-methyl-but-2-ene



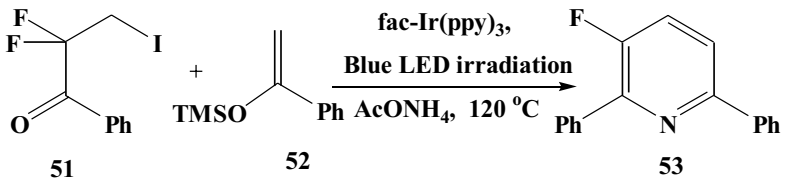
44 46 47

Scheme 10 Synthesis of pyridine from mixture ketone, enone and ammonia



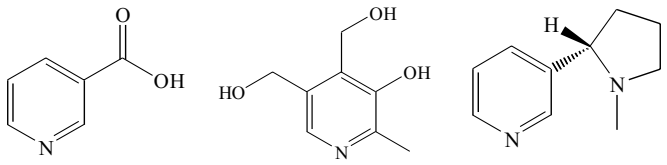
48a-b 49a-c 41 50a-c

Scheme 11 Synthesis of pyridine derivative α,α-difluoro-β-iodoketone



51 52 53

a member of alkaloids like nicotine 38. The toxicity of nicotine has a defensive function in nature and it is widely used for smoking cessation [64].



36 **37** **38**

Pyridine 2 itself is produced industrially by the traditional Chichibabin reaction (Scheme 6), wherein 2-methyl pyridine 44 was produced by the Bonnemann reaction, in which cobalt-catalyzed cyclotrimerisation of ethyne 42 and methyl nitrile 43 takes place as shown in Scheme 7. In addition, the aerobic gas-phase condensation of crotonaldehyde 45, formaldehyde 40 and ammonia 41 (Scheme 8) also affords compound 44. Likewise, numerous methods of synthesizing substituted pyridines have been reported [65].

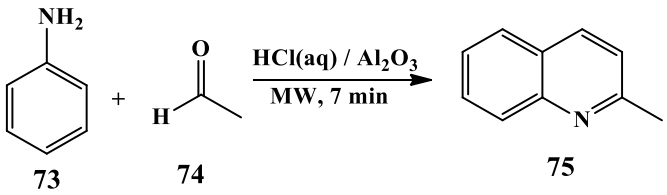
Moreover, the Lewis group developed a method for the synthesis of pyridine derivatives using chlorobis(cyclooctene)rhodium(I), dimer $[RhCl(coe)_2]_2$ and tricyclohexylphosphine hydrochloride $[PCy_3{\cdot}HCl]$ catalyst by intermolecular alkylation of 2-methyl pyridine 44 with 2-methyl-but-2-ene 46 via C–H bond activation to produce (S)-2-methyl-6-(3-methylbutan-2-yl)pyridine 47 as shown in Scheme 9 [66].

Disubstituted pyridines 50a–c are synthesized by treating a mixture of ketone 48a–b, enones 49a–c and ammonia 41 with magnesium methoxide as shown in Scheme 10. The reaction works particularly well with chalcones [67].

Interestingly, photo-redox coupling of α,α-difluoro-β-iodoketone 51 with silyl enol ether 52 in the presence of tris(2-phenylpyridine)iridium(III) [fac-Ir(ppy)$_3$] as catalyst under blue LED irradiation with subsequent one-pot condensation with ammonium acetate affords diversely substituted 3-fluoro-2,6-diphenylpyridine 53 as illustrated in Scheme 11 [68].

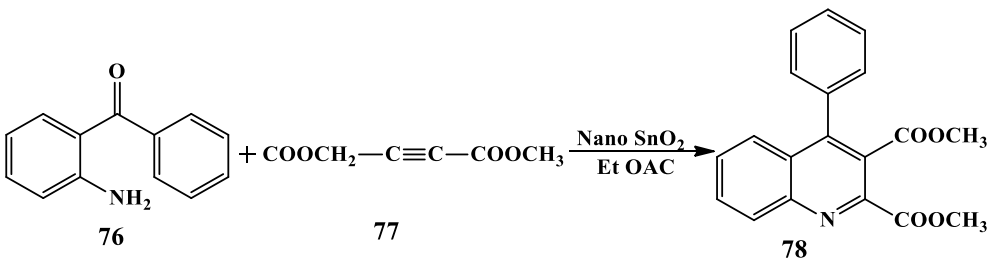
Pharmaceutical application of pyridine derivatives

Pyridine 2 corresponds to a huge group of compounds with applications as polymers, dyes, agrochemicals, antioxidants and pharmaceuticals [69]. One of the top-selling classes of pharmaceuticals containing the pyridine ring are the proton pump inhibitors and various drugs such as omeprazole 54, pantoprazole 55, lansoprazole 56 and rabeprazole 57 which are dwell in this area [70]. Other important species containing a pyridine moiety are pioglitazone 58 and rosiglitazone 59, which are members of the so-called thiazolidinedione class of type-2 diabetes drugs. These pharmaceutical drugs act as binders to the peroxisome proliferator-activated receptors that upon activation wander to the DNA to regulate the transcription of specific genes which control the metabolism of carbohydrates and fatty acids. The structures of compounds 58 and 59 show common structural features bearing a distal pyridine ring linked to the thiazolidinedione [69].



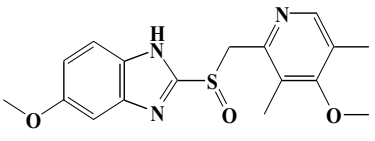
73 **74** **75**

Scheme 12 Synthesis of quinoline from quinaldine

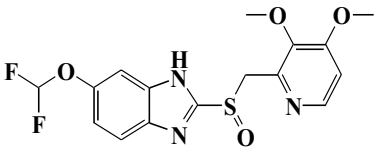


76 **77** **78**

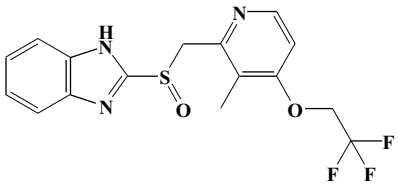
Scheme 13 Synthesis of quinoline from benzophenone



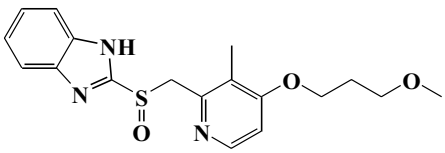
54



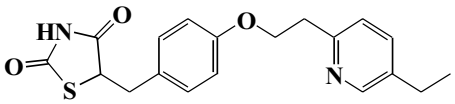
55



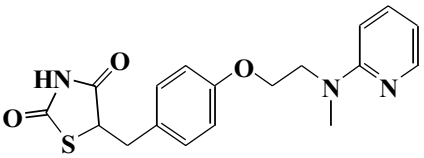
56



57

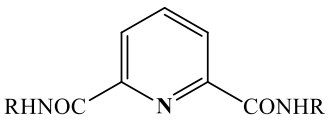


58



59

Pyridine derivatives as antibacterial agent Almeida et al. synthesized a series of C-2- and C-6-substituted pyridines 60a-d and evaluated them for in vitro against *P. aeruginosa*, *S. aureus*, *S. mutans* and *C. albicans* which exhibited a wide range of modest in vitro activity against the tested microorganisms [71].

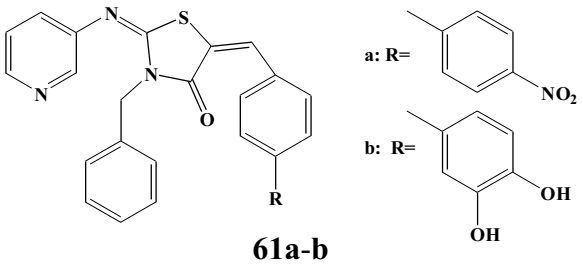


a: R= C_5H_5O **b:** R= OBn

c: R= Ph **d:** R= C_6H_4Br

60a-d

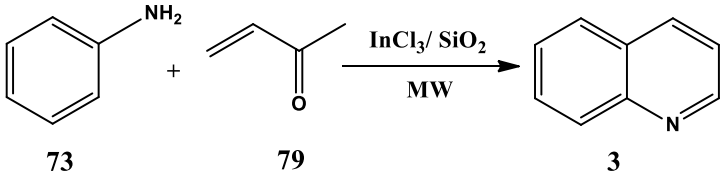
Pyridine derivatives as human carbonic anhydrase IX (CAIX) inhibitor and anticancer agent In order to obtain novel human CAIX inhibitors, a series of pyridine-thiazolidinone derivatives were synthesized by Ansari et al. The binding affinity of these compounds was measured by fluorescence binding studies and enzyme inhibition activity using an esterase assay of CAIX. It was observed that compounds 61a–b significantly inhibit the CAIX activity with the IC_{50} values, 1.61 μM and 1.84 μM, respectively. Further, they screened all the compounds for anticancer activity *in vitro* and found that compounds 61a–b showed considerable anticancer activity against human breast cancer cell (MCF-7) and human hepatocyte carcinoma (HepG-2) cell lines [72].



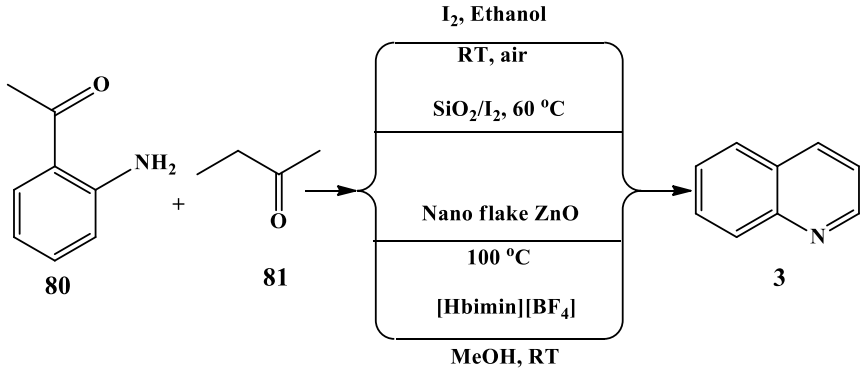
61a-b

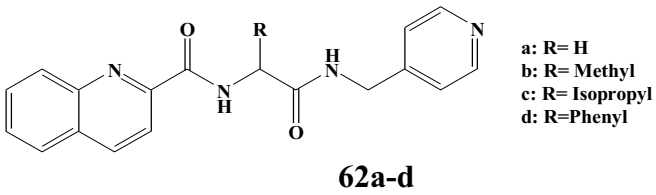
Pyridine derivatives as antifungal agent A series of compounds with amide-pyridine scaffolds 62a–d have been designed and synthesized by Bin Sun et al. to treat the increasing incidence of drug-resistant fungal infections.

Scheme 14 Synthesis of quinoline from aniline



Scheme 15 Synthesis of quinoline from ketone

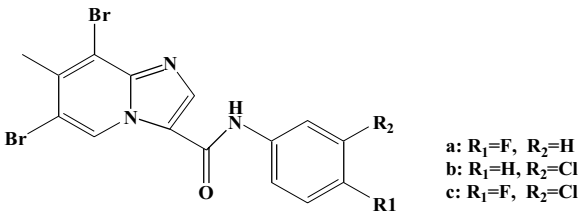




62a-d

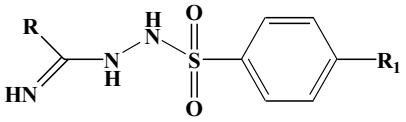
The in vitro evaluation results displayed that compounds 62a and 62b exhibited MIC values in the range of 0.125–2 µg/mL. This indicates that they have a broad spectrum of antifungal activity and excellent inhibitory activity against drug-resistant pathogenic fungi [73].

Pyridine derivatives as antitubercular agent A new derivatives of imidazo[1,2-a]pyridine has been synthesized successfully by Jadhav et al. and evaluated this series for antituberculosis activity. The biological results revealed that among the synthesized series, compounds 63a–c were found to be the most active with MIC of 12.5 µg/mL against mycobacterium tuberculosis (H37RV) strain [74].



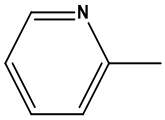
63a-c

Pyridine derivatives as anti-inflammatory and analgesic agents Sondhi et al. synthesis pyridine derivatives 64a–d and evaluated for anti-inflammatory activity and analgesic activity using quinolonen-induced paw edema assay and acetic acid writhing assay, respectively.

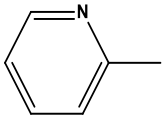


64a-d

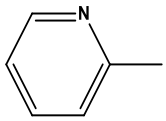
a: R= H, R_1=



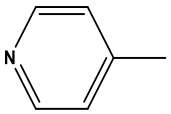
c: R= OCH_3, R_1=



b: R= CH_3, R_1=



d: R= OCH_3, R_1=

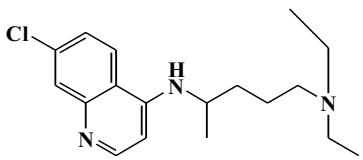


The biological results revealed that the compounds 64c and 64d have good anti-inflammatory, whereas compounds 64a, 64b and 64c showed good analgesic activity among the synthesized series [75].

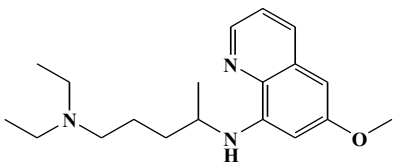
Introduction and synthesis of quinolone and its derivatives

Quinoline 3 and its analogues have always attracted both synthetic and biological chemist because of their assorted chemical and pharmacological efficacy. The structural hub of quinolone 3 has been synthesized by various conventional named reactions such as Skraup, Doebner-von Miller, Conrad Limpach, Friedlander, Pfitzinger and Combes synthesis [76].

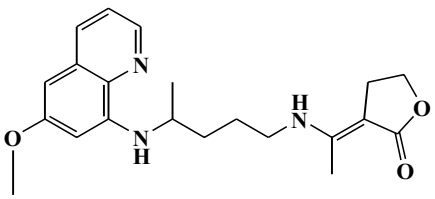
Moreover, the quinolone ring system occurs in several natural compounds, particularly in alkaloids and is repeatedly used for the design of many synthetic compounds with various pharmacological possessions. The number of natural products bearing quinolone skeleton, used as a medicine or employed as lead molecule for the development of newer and potent molecules [77]. Recently, our research group has also synthesized many quinolone derivatives, which are also having biological importance [78]. Besides, there are a few promising compounds with the quinolone ring, like chloroquine 65, pamaquine 66, bulaquine 67, tafenoquine 68, quinine 69 and mefloquine 70 employed as an antimalarial agent. Whereas amodiaquine 71 used as an anti-inflammatory as well as an antimalarial agent [79, 80].



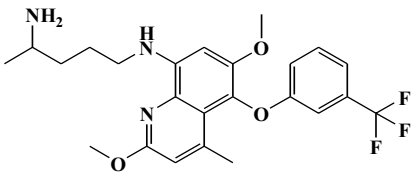
65



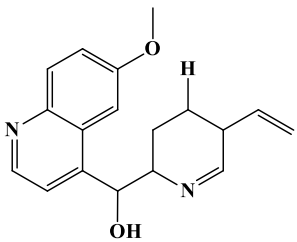
66



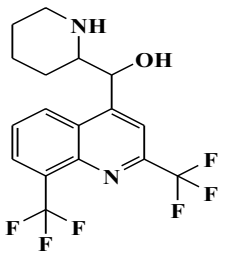
67



68

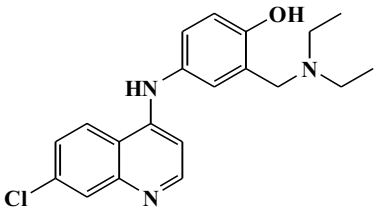


69

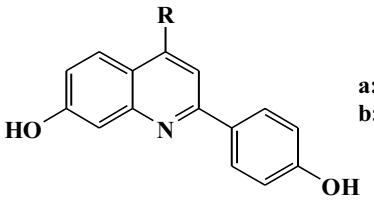


70

Correspondingly, the 2-arylquinoline derivatives 72a and 72b show selectivity in binding to the estrogen receptor b, which plays an important role in the development, maintenance and function of the mammalian reproductive system, as well as in non-sexual tissues [81, 82].



71



a: R= CH=CH$_2$
b: R= NH$_2$

72a-b

Fascinatingly, Safari et al. described the synthesis of quinaldine 75 by the reaction of aniline 73 with acetaldehyde 74 under microwave (MW) induced method without any solvent (Scheme 12) [83]. This method was tried with different Bronsted acids, but it was found to be the best with hydrochloric acid as a catalyst, which afforded highest yield. This method was found to be simple and useful because of high yield, a straight forward, short reaction time and easy work-up procedure.

On the other hand, Qandalee et al. synthesized dimethyl-4-phenylquinoline-2,3-dicarboxylate 78 by two-component reaction of 2-aminobenzophenone 76 with acetylenic diester 77 under mild conditions using nano-stannous oxide as catalyst as shown in Scheme 13 [84].

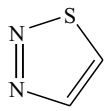
A simple and efficient method for the synthesis of quinolone 3 was developed by Ranu et al. [85] as one-pot reaction of aniline 73 with methyl vinyl ketone 79 on the surface of a silica gel inseminated with indium (III) chloride ($InCl_3/SiO_2$) under MW irradiation without any solvent (Scheme 14).

A mild and efficient methods for the synthesis of quinolone 3 by utilizing o-amino acetophenone 80 and enolisable ketone 81 with molecular iodine as a catalyst in ethanol was achieved [86]. Similarly quinolone 3 was obtained by combining compounds 80 and 81 in presence of iodine and silica gel under solvent-free conditions [87]. A Friedlander heteroannulation method was also used for the same synthesis using nano-zinc oxide as a mild, non-volatile, non-corrosive and efficient catalyst which provides regiospecific synthesis under solvent-free conditions [88]. Moreover, using Bronsted-acidic ionic liquid [Hbim][BF_4] under ultrasound technique at room temperature afforded the same quinolon 3 as illustrated in Scheme 15 [89]. These procedures avoid the use of dangerous acids or bases which leads to a harsh reaction environment. The advantages of these methods include generality of good substrate, inexpensive reagents and catalysts under mild conditions [90].

Pharmaceutical application of quinoline derivatives

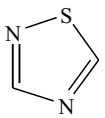
Quinoline derivatives as anticancer agent A series of indole-fused quinoline derivatives have been synthesized and evaluated for anticancer activity by Vittorio et al. [91] and observed that among the series compound 82 acts on telomerase with IC_{50} value as 16 μM. Similarly, Kemnitzer et al. recognized novel quinoline derivatives as an apoptosis inducer through caspase and cell-based high-throughput screening assay. This study indicated that 1-(4-(1*H*-imidazol-1-yl)benzoyl)-3-cyanopyrrolo[1,2-*a*]quinoline 83 was found to be highly active against human breast cancer cells T47D, human colon cancer cells HCT116 and hepatocellular carcinoma cancer cells SNU398 [92].

Fig. 1 The four isomeric form of thiadiazole



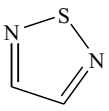
[1, 2, 3]-Thiadiazole

90



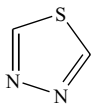
[1, 2, 4]-Thiadiazole

91



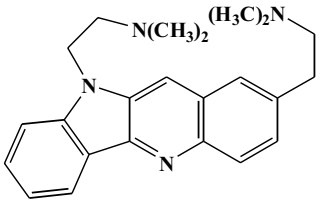
[1, 2, 5]-Thiadiazole

92

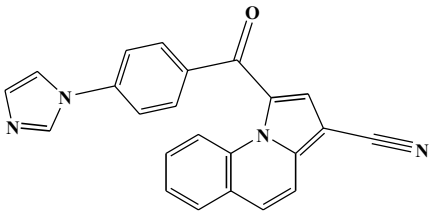


[1, 3, 4]-Thiadiazole

4



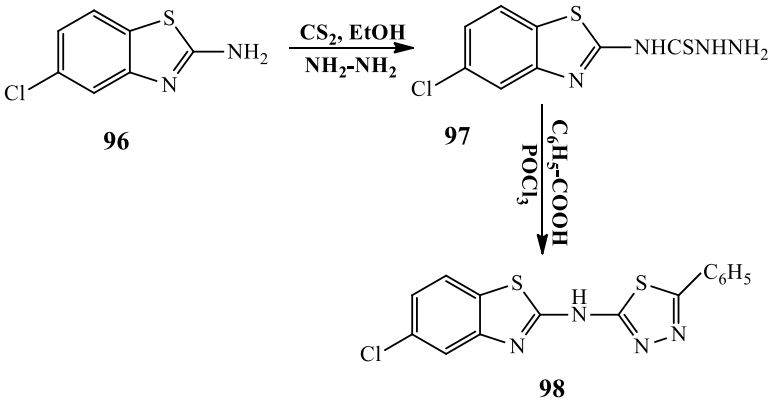
82



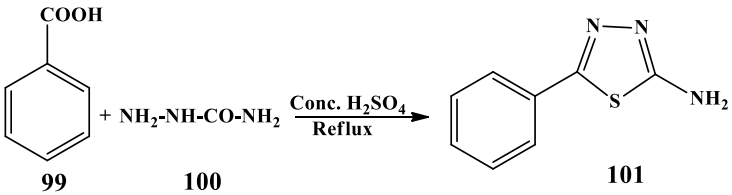
83

Quinoline derivatives as antimicrobial agent Quinolone is a special structural class of antimicrobial agent [93]. A novel 2-amino-4-(8-quinolinol-5-yl)-1-(p-tolyl)-pyrrole-3-cabonitrile 84 was annulated to fused analogues such as pyrrole and quinolone system by Abdel-Mohsen et al. [94] and screened for in vitro antimicrobial activities against two strains of bacteria and fungi. The compound showed moderate-to-good activity.

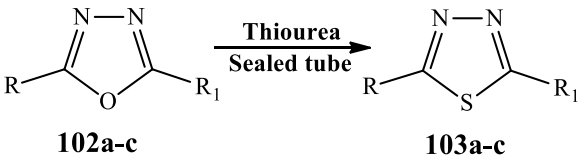
Scheme 16 Synthesis of [1,3,4]-thiadiazole from semicarbazide



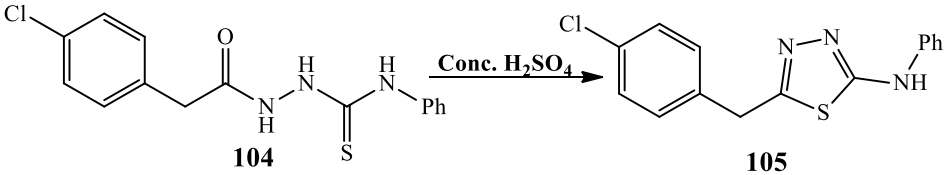
Scheme 17 Synthesis of [1,3,4]-thiadiazole from mixture of benzoic acid and thiosemicarbazine

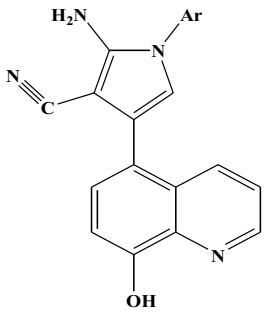


Scheme 18 Synthesis of [1,3,4]-thiadiazole from oxidazole



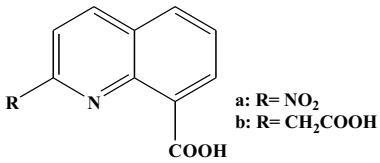
Scheme 19 Synthesis of [1,3,4]-thiadiazole from carbothioamide



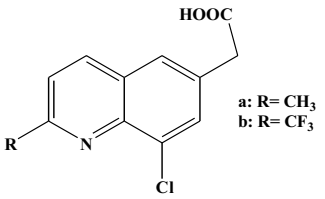


84

Quinoline derivatives as anti-inflammatory agent Non-steroidal anti-inflammatory drugs (NSAIDs) have an extensive clinical application for the treatment of inflammatory and painful conditions. Quinoline moiety with acidic function were reported by Kohno et al. [96, 97] as novel substituted 1,2,3,4-tetrahydroquinoline derivatives and evaluated for disease modifying anti-rheumatic drugs. Out of the synthesized series, compounds 86a–b and 87a–b significantly suppressed the swelling of the adjunct arthritic rat paw at doses less than 25 mg/kg (acute/chronic).

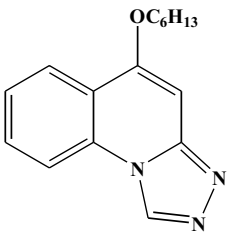


86a-b



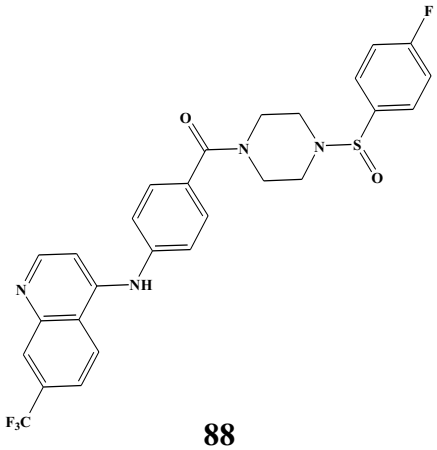
87a-b

Quinoline derivatives as anticonvulsant agent In recent years, various molecular modifications of quinoline derivatives have been reported with promising anticonvulsant results. For instance, Guo et al. [95] reported a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives with anticonvulsant activity evaluated by the maximal electroshock test and their neurotoxicities were measured by the rotarod test. They found that in this sequence 5-(hexyloxy)-[1,2,4]triazolo[4,3-a]quinoline 85 is the most potent anticonvulsant, with median effective dose (ED_{50}) of 19.0 mg/kg.

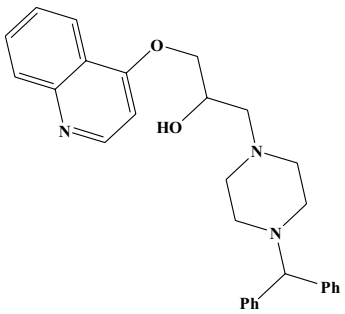


85

Quinoline derivatives as cardiovascular agent In an effort to recognize the potential cardiovascular agent as calcium channel blocker, cyclic adenosine monophosphate (cAMP) phosphodiesterase III, etc., a range of chemical alteration of quinoline derivatives has been attempted with positive results and have come up with new lead compounds. In this regard, the synthesis and SAR study on a series of amino quinoline derivatives and evaluation for their hypotensive activity was reported by McCall et al. [98]. In this sequence, [4-(4-fluoro-benzenesulfinyl)-piperazin-1-yl]-[4-(7-trifluoromethyl-quinolin-4-ylamino)-phenyl]-methanone 88 was selected for clinical development based on its hypotensive effect in rat, cat and dog. However, 1-(4-benzhydryl-piperazin-1-yl)-3-(quinolin-4-yloxy)-propan-2-ol 89 showed potent inotropic effect in rat heart [99].



88



89

Introduction and synthesis of [1,3,4]-thiadiazole and its derivatives

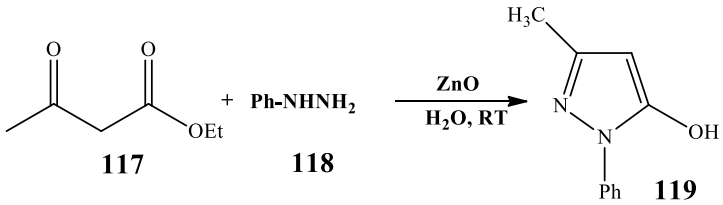
Generally, five-membered aromatic systems having three heteroatoms at symmetrical position have been studied because of their physiological properties [100]. Thiadiazole is a heterocyclic compound containing two carbon atoms, two hydrogen atoms, two nitrogen atoms and one sulfur atom as a part of the aromatic five-membered diunsaturated ring structure having molecular formula $C_2H_2N_2S$ [101]. It is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as a hydrogen binding domain and two electron donor system [102]. Further, thiadiazoles act as a bioisosteric replacement of thiazole moiety. It is also a bioisosteres of oxadiazole and oxazole. Substitution of these heterocyclic compounds with a thiadiazole typically leads to analogues with improved activities because the sulfur atom imparts improved liposolubility [103]. It has been observed that differently substituted thiadiazole moieties have different activity [104].

The incorporation of oxygen, nitrogen and sulfur donor atoms in the macrocycles noticeably affect their complexing properties because of the hard (O, N) and soft (S) character of the donor atoms and the exodentate tendency of the sulfide linkages [105]. In the recent years, there has been prominent exploration of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [106], antitubercular, anticonvulsants, anti-inflammatory, antihypertensive [107], antioxidant, human adenosine A3 antagonist [108], anticancer [109, 110] and antifungal activities [111]. Thiadiazole displays an important role in nature as the thiazolium ring, present in vitamin B-1, serves as an electron link and its coenzyme form is essential for the decarboxylation of α-keto acids [112].

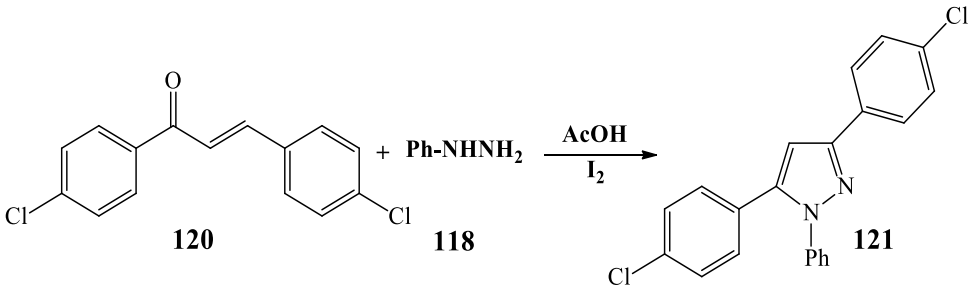
Thiadiazole occurs in nature in four isomeric forms as [1–3]-thiadiazole 90, [1,2,5]-thiadiazole 91, [1,2,4]-thiadiazole 92 and [1,3,4]-thiadiazole 4 as shown in Fig. 1. The most fully investigated of these being the [1,2,4]- and [1,3,4]-thiadiazoles.

The [1,3,4]-thiadiazole nucleus is one of the most important and well known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Many drugs containing [1,3,4]-thiadiazole nucleus such as acetazolamide 93, methazolamide 94 and megazol 95 are available in the market [113, 114].

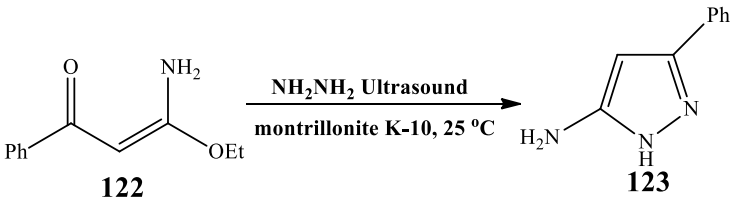
Scheme 20 Synthesis of pyrazole from mixture of phenylhydrazine with ethyl acetoacetate



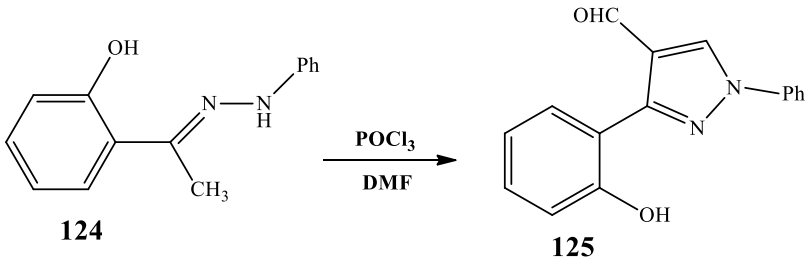
Scheme 21 Synthesis of pyrazole from α, β-ethylenic ketone

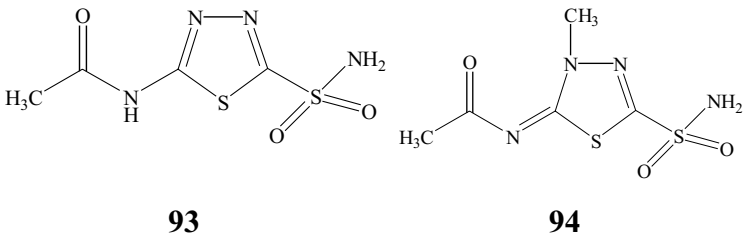


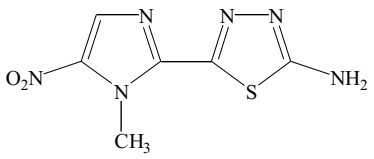
Scheme 22 Synthesis of pyrazole from (E)-3-amino-3-ethoxy-1-phenylprop-2-en-1-one



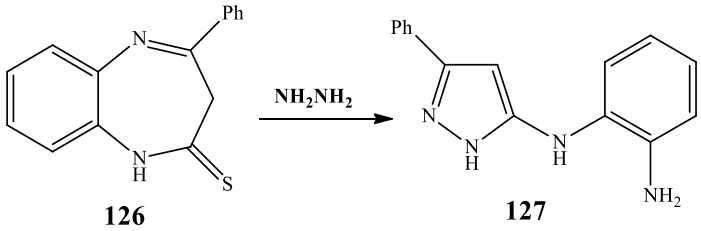
Scheme 23 Synthesis of pyrazole from Vilsmeier-Haack reaction





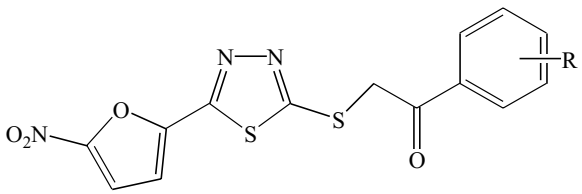


Scheme 24 Synthesis of pyrazole from benzodiazepine-2-thione



126 127

The development of [1,3,4]-thiadiazole chemistry is linked to the discovery of hydrazine and phenylhydrazine in the late nineteenth century. Commonly, [1, 3, 4]-thiadiazoles can be available via general routes from cyclization of acylhydrazines including N,N′-diacylhydrazines and monoacylhydrazines or transformation from [1,3,4]-oxadiazoles. The normal or classical process of synthesis of thiadiazoles includes the condensation of thiosemicarbazides with carboxylic acids or carboxylic acid chlorides or carboxylic acid esters with cyclizing or condensing agents such as phosphorus oxychloride, phosphorus pentachloride, acetic anhydride and sulfuric acid etc. For instance, the reaction of 6-chloro-1,3-benzothiazol-2-yl semicarbazide 97 and aromatic acid in $POCl_3$ produces compound 98 in good yield. The precursor 97 was obtained by the reaction of 6-chloro-2-amino benzothiazole 96, carbon disulfide (CS_2) and hydrazine hydrate in ethanol and ammonia solution as illustrated in Scheme 16. Besides, the synthesized thiadiazole 98 has shown significant antimicrobial activity [115].



106a-c

a: R= 2-Cl
b: R= 3-Cl
c: R= 4-Cl

Pattan et al. reported the synthesis of 2-amino-5-phenyl-[1,3,4]-thiadiazole 101 by refluxing a mixture of benzoic acid 99 and thiosemicarbazine 100 with concentrated sulfuric acid for 3–4 h [116] as represented in Scheme 17.

On the other hand, 2,5-diaryl-1,3,4-thiadiazole derivatives 103a–c were synthesized from the transformation process by heating 2,5-diaryl-[1,3,4]-oxadiazole derivatives 102a–c with thiourea using tetrahydrofuran as a solvent in a sealed test tube, maintaining the temperature about 120–500 °C, for 25–30 h in an oil bath [117] as described in Scheme 18.

As well, from arylhydrazide, Desai et al. synthesized various thiadiazole analogues. For instant, 5-(4-chlorobenzyl)-N-phenyl-[1, 3, 4]-thiadiazol-2-amine 105 was obtained by the cyclization of 2-[2-(4-chlorophenyl)acetyl]-N-phenylhydrazinecarbothioamide 104 with sulfuric acid as represented in Scheme 19 [118].

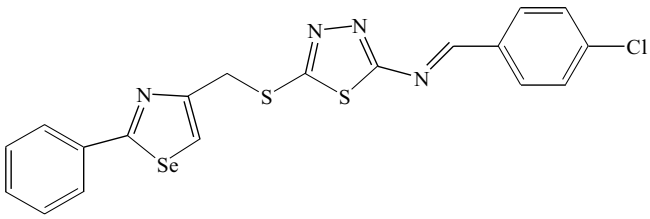
Pharmaceutical application of [1,3,4]-thiadiazole derivatives

[1,3,4]-Thiadiazole derivatives as antihelicobactor pylori agent It is currently recognized that *Helicobacter pylori*, an S-shaped spiral microaerophilic gram-negative bacterium first isolated in human gastric mucosa in 1982. It is the main cause of gastric and duodenal ulcers, and gastric cancer. Hence, the World Health Organization has proposed *H. pylori* as a class 1 carcinogen in humans [119].

To overcome these effects, Foroumadi et al. have been introduced a series of 2-alkylthio-5-(nitroaryl)-[1,3,4]-thiadiazole derivatives 106a–c and evaluated their in vitro antihelicobactor pylori activity and also studied the structure–activity relationship. They found that these nitrofuran analogues 106a–c had shown the potent activity [120].

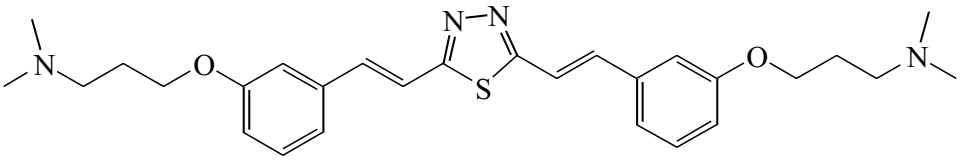
[1,3,4]-Thiadiazole derivatives as anticancer agent Cancer is not just a single disease, but a group of multiple diseases

characterized by inappropriately controlled cell proliferation and replication eventually resulting in disruption of normal physiology, metabolism or structure [121]. It is one of the leading diseases claiming numerous lives and consequently responsible for high mortality rates across the globe [122]. Attracted by these information, Zhao et al. have been synthesized and represented a novel series of 1,3-selenazole-containing [1,3,4]-thiadiazole derivatives bearing Schiff base moieties and evaluate for their in vitro antiproliferative activities against MCF-7 and mouse lymphocyte leukemia cell (L1210) by cell counting kit-8 assay [123]. In particular, in the synthesized series, compound 107 was the most potent compound.



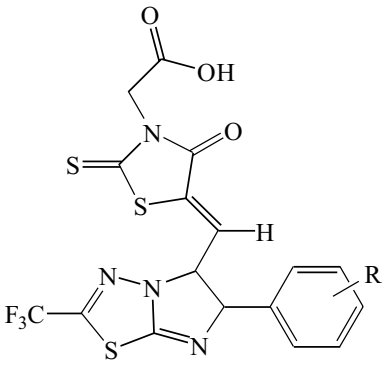
107

In addition, compound 108 was reported to induce the early-phase apoptosis in adenocarcinomic human alveolar basal epithelial cells (A549cells) via the B-cell lymphoma-extra large (Bcl-XL) down-regulation [124].



108

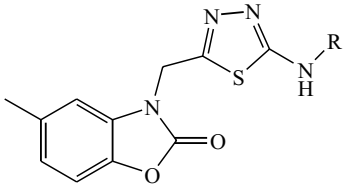
[1,3,4]-Thiadiazole derivatives as antitubercular agent With an aim of identifying new antitubercular drug candidates, Alegaon et al. have been synthesized a new class of 2-(trifluoromethyl)-6-arylimidazo[2,1-b][1,3,4]-thiadiazole analogues 109a-f by both conventional and MW-assisted method and tested for their in vitro antitubercular activity against H37Rv. Moreover, various drug-like properties of these new compounds were predicted. Some compounds from this series exhibited good activity with MIC in the range 3.12–1.56 µg/ml and researcher suggests that these may serve as promising lead scaffolds for further generation of new antitubercular agent [125].



a: R= H
b: R= Cl
c: R= Br
d: R= CH_3
e: R= OCH_3
f: R= NO_2

109a-f

[1,3,4]-Thiadiazole derivatives as anti-inflammatory agent Goksen et al. synthesized and screened the anti-inflammatory activity of various 2- benzoxazolinone [1,3,4]-thiadiazole derivatives 110a–c. Also, reported that in the synthesized series phenyl substituted compound 110c exhibited the most potent anti-inflammatory activity [126].

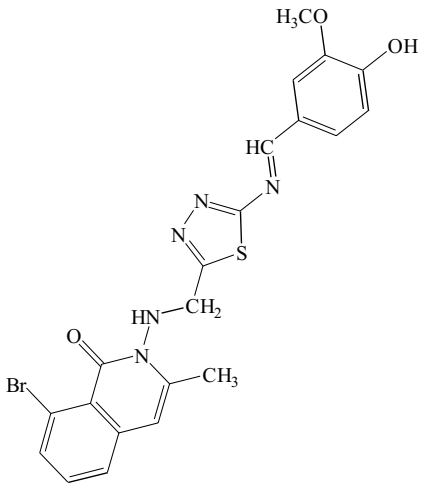


a: R= CH_3
b: R= C_2H_5
c: R= C_6H_5

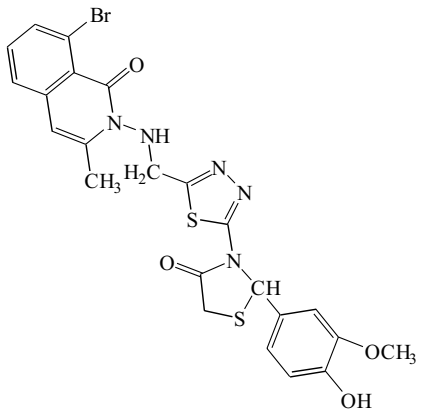
110a-c

[1,3,4]-Thiadiazole derivatives as anticonvulsant agent Epilepsy is a common and diverse set of neurological disorders characterized by seizures. Anticonvulsants are more accurately called antiepileptic drugs (AED)

[127, 128]. Remarkably, [1,3,4]-thiadiazole derivative acetazolamide, i.e., 2-acetyl amido-1,3,4-thiadiazole-5 sulfonamide was first used as an AED in 1952 [129]. In this connection, Archana et al. reported compounds 111 and 112, which exhibited the same or even a better anticonvulsant degree than the reference drug phenytoin sodium, sodium valproate and lamotrigine in the maximal electroshock or pentylenetetrazol test [130, 131].



111

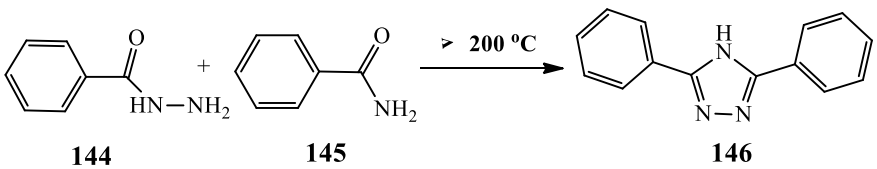


112

Introduction and synthesis of pyrazole and its derivatives

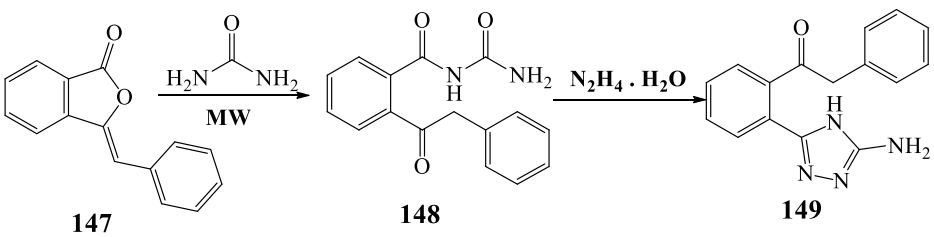
Pyrazole 5 is a chemical compound of synthetic origin that have a five-membered heterocycle with two nitrogen atoms and three adjacent carbon atoms. Several members of the pyrazole class have shown good pharmacological effects or have the potential biological activities, such as, anti-inflammatory [132], antiviral [133], antimicrobial [134], anticonvulsant [135], antitumour [136], fungicidal [137] and antihistaminic activities [138]. The pyrazole moiety has an important role in some drug structure, for example, some arylpyrazole derivatives have anti-HIV activity [139–141] and some pyrazole-3-carboxamide moiety has antiCB1cannabinoid ability [142]. In addition, the pyrazole derivatives have various significance on crop protection chemistry. To mention a few compounds like fipronil 113 as herbicidal, penthiopyrad 114 as fungicidal and fluazolate 115 as insecticidal, which are all active pyrazole derivatives. In this connection, pyrazole derivatives have attracted much attention of chemists [143].

Scheme 25 Synthesis of pyrazole from benzohydrazide with benzamide

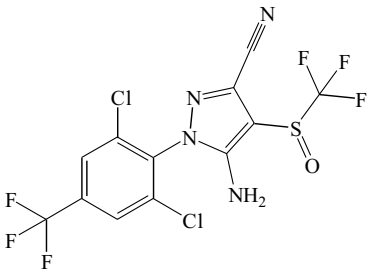


144 145 146

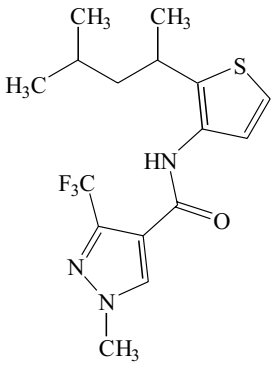
Scheme 26 Synthesis of pyrazole from 3-benzylidene phthalide



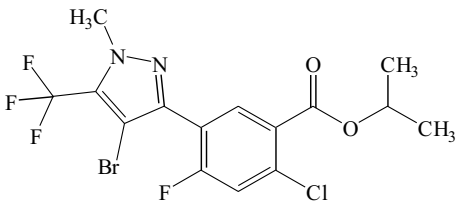
147 148 149



113

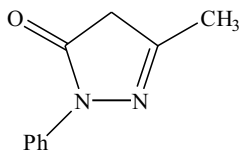


114



115

Knorr [144, 145] first synthesized pyrazole derivative in 1883 by the reaction of ethyl acetoacetate with phenyl hydrazine, which yielded 1-phenyl-3- methyl-5-pyrazolone 116.



116

Then Knorr [146] introduced the name pyrazole for this compound to denote that the nucleus was derived from pyrrole by the replacement of a carbon by nitrogen.

An efficient nano-zinc oxide catalyzed green protocol for the synthesis of 1,3,5-substituted pyrazole derivative 119 by condensation of phenylhydrazine 118 with ethyl acetoacetate 117 was described as shown in Scheme 20. The main advantage of this protocol is the excellent yield, short reaction time and easy work procedure [147].

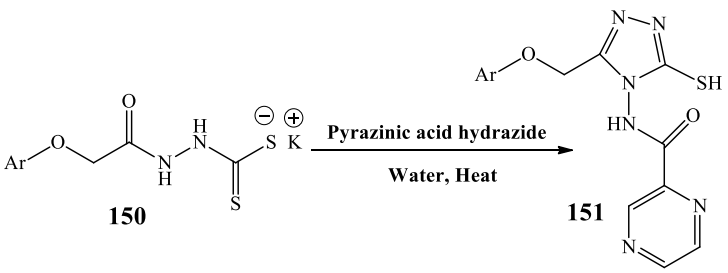
A method for the synthesis of 1,3,5-trisubstituted pyrazoles from an α, β-ethylenic ketone was also described. Cyclocondensation of the α, β-ethylenic ketone 120 with phenylhydrazine 118 in acetic acid and presence of iodine afforded 3,5-bis(4-chlorophenyl)-1-phenyl-1H-pyrazole 121 in good yield as represented in Scheme 21 [148].

Wherein 5-amino-3-phenylpyrazole 123 was prepared from (E)-3-amino-3-ethoxy-1-phenylprop-2-en-1-one 122 using montmorillonite K-10 clay under sonication conditions as illustrated in Scheme 22 [149].

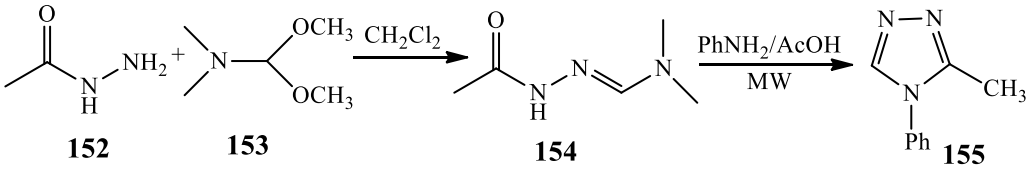
Interestingly, Vilsmeier-Haack reaction was employed to synthesize 3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde 125 by condensation of a (E)-2-[1-(2-phenylhydrazono)ethyl]phenol 124 in the presence of phosphorus oxychloride as illustrated in Scheme 23 [150].

Ferfra et al. prepared substituted pyrazole 127 from benzodiazepine-2-thione 126 in one step by opening the

Scheme 27 Synthesis of pyrazole from potassium dithiocarbazinate



150 **151**



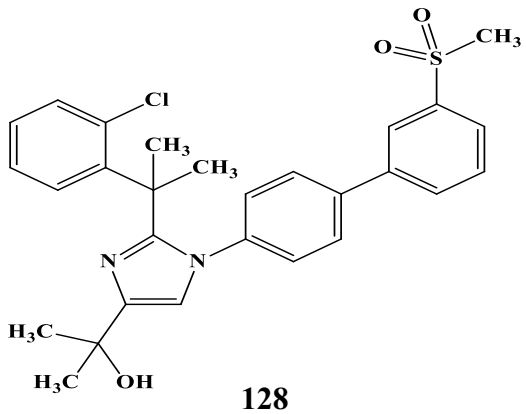
Scheme 28 Synthesis of pyrazole from mixture of acetohydrazide and acetal

seven-membered ring of this compound with hydrazine to achieve N^1-(3-phenyl-1H-pyrazol-5-yl)benzene-1,2-diamine 127 as shown in Scheme 24 [151].

Pharmaceutical application of pyrazole derivatives

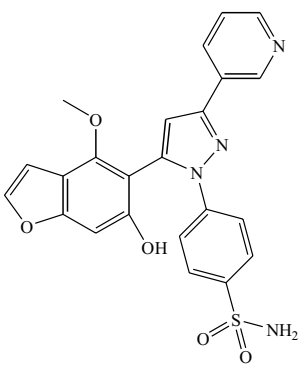
Pyrazole derivatives as antihypercholesterolemic agent The presence of high levels of cholesterol in blood is termed as hypercholesterolemia or dyslipidemia. An increased level of lipoproteins (carrying cholesterol) other than high-density lipoprotein may increase the risk of atherosclerosis and coronary heart disease [152]. In order to reduce the cholesterol production or absorption, lipid lowering medication is mainly required [153]. Some of the antihypercholesterolemic compounds based on pyrazole scaffold have been reported by various researchers.

For instance, Kick et al. developed a series of biaryl pyrazoles and evaluated them for antihypercholestrolemic potential. Among the biaryl pyrazole series, compound 128 was identified as the selective partial agonist for liver X receptor b with potent induction of ATP binding transporters in human blood [154].

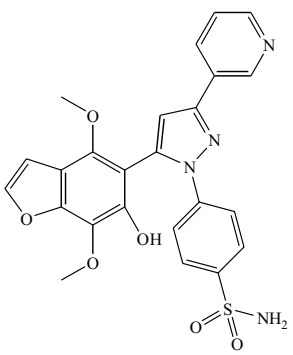


128

Pyrazole derivatives as anti-inflammatory agent A series of celecoxib analogues with the inclusion of benzofuran moiety were synthesized and evaluated for in vitro cyclooxygenase-1 and cyclooxygenase-2 (COX-1/COX-2) inhibitory activity. Among the series, compounds 129 and 130 exposed the highest anti-inflammatory activity. Also, results revealed that a contributory role of these compounds bearing C-3-pyridine-3-yl exhibits good anti-inflammatory efficiency in animal models [155].

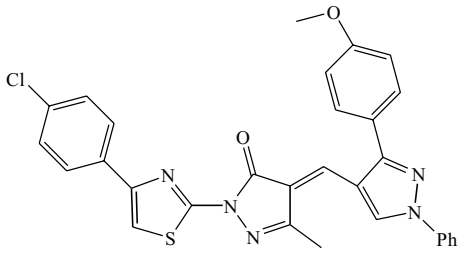


129



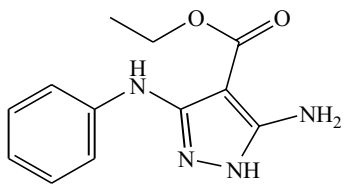
130

Recently, a new group of pyrazole derivatives were designed for the evaluation as selective COX-2 inhibitors. The results indicated that the compound 131 exhibited significant COX-II inhibition [156].



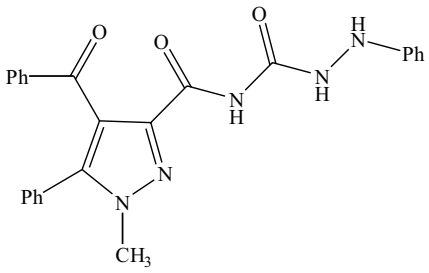
131

Pyrazole derivatives as antimalarial agent Dominguez et al. investigated antimalarial activity of novel substituted pyrazole derivatives against *P. falciparum*. Significant activity was displayed by ethyl 5-amino-3-(phenylamino)-1H-pyrazole-4-carboxylate 132 [157].



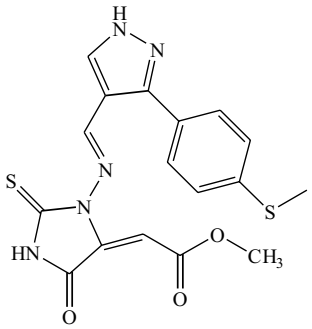
132

Pyrazole derivatives as antibacterial and antifungal agents A series of 1H-pyrazole-3-carboxylic acid derivatives were synthesized and evaluated for their antibacterial activity against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas putida*. The results showed that the compound 133 was the best compound in the synthesized series, which exhibited antibacterial activity against both gram-positive and gram-negative bacteria [158].

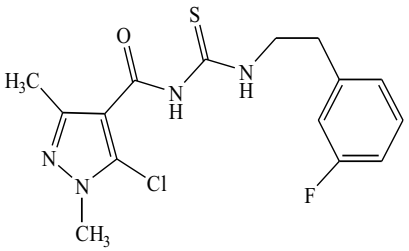


133

Further, a series of novel imidazole derivatives containing substituted pyrazole moiety were synthesized by Vijesh et al. and screened for antifungal and antibacterial activities. Among the synthesized sequence, compound 134 was found to be potent antimicrobial agent [159]. In addition, several pyrazole acyl thiourea derivatives were synthesized and evaluated for antifungal activity against *G. zeae, F. oxysporum* and *C. mandshurica*. Among them compound 135 displayed good antifungal activity against all the tested fungi [160].



134

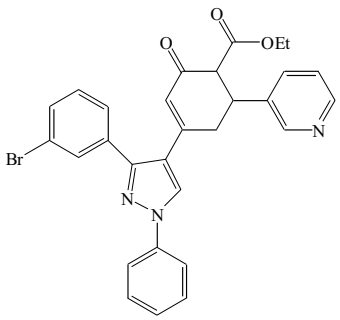


135

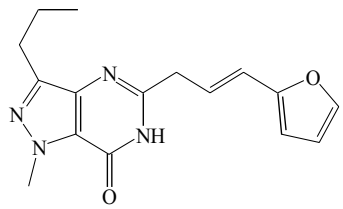
Pyrazole derivatives as anticancer agent Remarkably, Alam et al. synthesized a sequence of pyrazole derivatives and evaluated for topoisomerase IIa inhibitory activity. Further, the same sequence was subjected to in vitro cytotoxicity against a panel of cancerous cell lines (Human breast cancer cell line MCF-7, human non-small cell lung carcinoma-NCI-H460 and human cell line derived from cervical cancer cells-HeLa) and human embryonic kidney 293 cells (HEK-293 T). In this sequence, compound 136 showed a superior cytotoxicity with an IC_{50} value of 7.01 μM for HeLa, 8.55 μM for NCI-H460 and 14.31 μM for MCF-7 cancer cell lines [161]. Also, Shi et al. synthesized a series of pyrazole-carboxamide derivatives and evaluated for anticancer activity. The results exhibited that compound 137 was found to be a strong anticancer agent against glycyrrhiza can induce human gastric cancer-MGC-803 cells line, and also exhibited the most potent telomerase inhibitory activity [162].

Besides, its potentiation effects on the cytotoxicity on both cisplatin and doxorubicin, it also exhibited marked antitumour activity as a single agent in breast cancer bearing animals [163].

Pyrazole derivatives as anti-Alzheimer's agent Alzheimer's disease (AD) is one of the most common types of dementia and it is the most prevalent neurodegenerative disorder in the world, as approximately 47 million people are affected by this disease [164]. AD is an irreversible, a progressive brain disorder that slowly destroys memory and thinking skills. Age is the greatest non-genetic risk factor among all [165, 166]. It causes functional as well as structural disturbance of brain's nerve cells. In an effort to develop novel inhibitors of receptor for advanced glycation end products for the treatment of Alzheimer's disease,

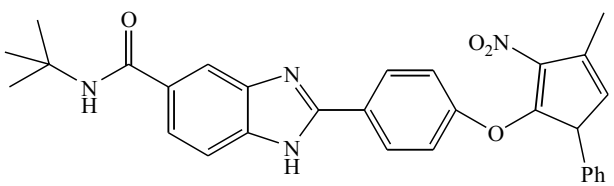


136



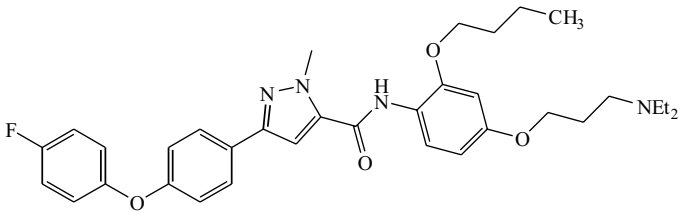
137

Additionally, Galal et al. described the synthesis of pyrazole-benzimidazole derivatives as novel potent active checkpoint kinase 2 (Chk2) inhibitors. Out of the synthesized derivatives, compound 138 was reported to be having the most potent effects toward Chk2 inhibition with cytotoxic properties.



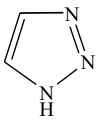
138

a series of pyrazole-5-carboxamides were synthesized by Han et al. and evaluated for anti-Alzheimer's activity. Results indicated that compound 139 is the most active compound among the synthesized series, which exhibited higher inhibitory activity, and also exhibited significant brain Aβ-lowering effects as well as favorable aqueous solubility [167].



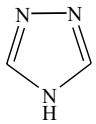
Introduction and synthesis of [1,2,4]-triazole and its derivatives

Many five-membered rings with three hetero atoms at symmetrical positions of aromatic systems have been studied because of their interesting physiological properties [168, 169]. The act of imidazole moiety is a prominent in medicinal chemistry and has led to the emergence of triazole derivatives. Triazoles are the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen [170]. Triazole exists in two isomeric forms, namely [1–3]-triazole 140 and [1,2,4]-triazole 6, as shown below [171].



[1,2,3]-Triazole

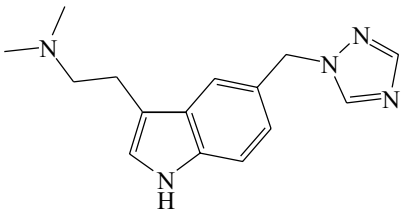
140



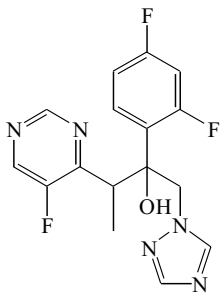
[1,2,4]-Triazole

6

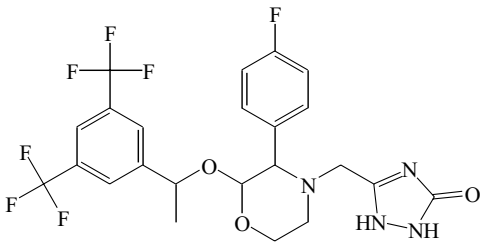
Previous studies indicates that [1–3]-triazole derivatives are used as antibacterial [172–175], antifungal [175, 176], antioxidant [177], antimalarial and antileishmanial agents [178, 179]. Moreover, [1,2,4]-triazole 6 is used as a factor in drug structures, even more than [1–3]-isomer 140. The chemical industry got attention in the synthesis of both simple and fused [1,2,4]-triazole systems [180–185], after finding some of 1,2,4-triazoles have the capability of inhibiting the fog in photographic emulsions [186] and some others being useful herbicides and convulsants [187]. Some of the [1,2,4]-triazole drugs like rizatriptan benzoate (Maxalt) 141 an antimigraine medication, voriconazole (Vfend) 142 an antifungal, and aprepitant (Emend) 143 for chemotherapy induced nausea and vomiting are well documented. Besides, they also appear in analytical and industrial chemistry [170].



141



142



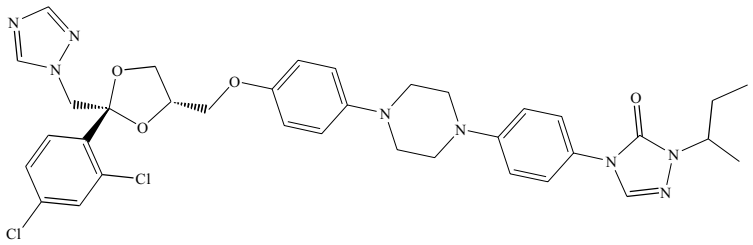
143

The 3,5-disubstituted-[1,2,4]-triazoles was first synthesized by the thermal condensation of benzohydrazide 144 with benzamide 145, to yield the diphenyl-[1,2,4]-triazole 146 as delivered in Scheme 25. This reaction is called as Pellizari reaction [188].

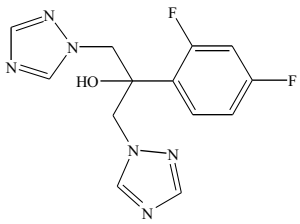
The reaction of 3-benzylidene phthalide 147 with urea under MW induced method to afford 1-(2-(α- phenylacetyl) benzoyl)urea 148 as an intermediate, which on treatment with hydrazine hydrate furnish 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone 149 was reported in good yield as shown in Scheme 26 [189].

Pharmaceutical application of [1,2,4]-triazole derivatives

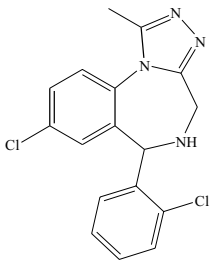
In the current years, the chemistry of triazoles and their fused heterocyclic derivatives have received significant consideration owing to their synthesis and effective biological importance. For example, a large number of [1,2,4]-triazole 6 containing ring system has been incorporated into a wide variety of therapeutically interesting drug candidates, including CNS stimulants [192], antioxidant [193], anticancer [194] and antitubercular [195] agents. As a matter of fact, antimycotic active [1,2,4]-triazole compounds inhibit the biosynthesis of ergosterol by blocking 14-a-demethylation such as itraconazole 156 and fluconazole 157.



156



157

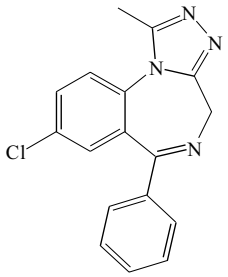


158

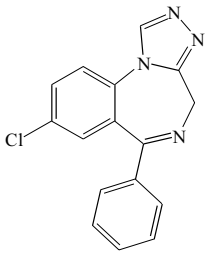
Apart from this, pyrazinyl substituted 5-mercapto-[1,2,4]-triazole 151 was prepared by Udupi et al. in the year 2007 from the corresponding potassium dithiocarbazinate 150 in the presence of pyrazinic acid hydrazide as shown in Scheme 27 [190].

An efficient MW assisted one-pot and three component synthesis of 3-methyl -4-phenyl-4H-[1,2,4]-triazole 155 was reported by Li et al. This reaction was accomplished by the reaction of acetohydrazide 152 with *N,N*-dimethylformamide dimethyl acetal 153 and primary amine in the presence of acetic acid. This reaction occurred via an intermediate (E)-N'-acetyl-N,N-dimethylformohydrazonamide 154 as depicted in Scheme 28 [191].

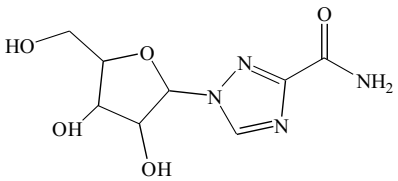
In addition, there are known drugs containing the [1,2,4]-triazole group, like triazolam 158 used to treat a certain sleep problem (insomnia), alprazolam 159 used in short-term management of anxiety disorders, specifically panic disorder, estazolam 160 is used for short-term treatment of insomnia and ribavirin 161 is a broad spectrum antiviral agent which is active against both RNA and DNA viruses and tract viral disease. Nowadays, combination of interferon-ribavirin is used for the treatment of hepatitis-C.



159

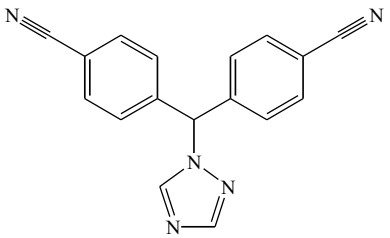


160

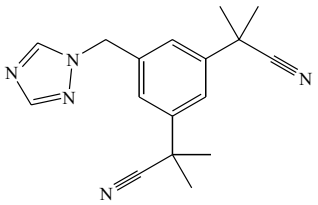


161

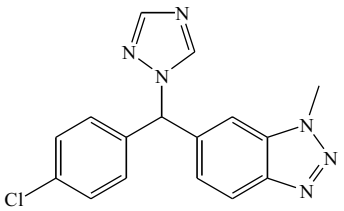
Nevertheless compounds, letrozole 162, anastrozole 163 and vorozole 164 also have [1,2,4]-triazole nucleus and are very effective as aromatase inhibitors [196].



162

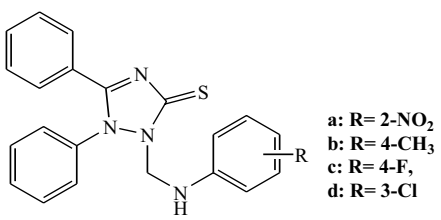


163



164

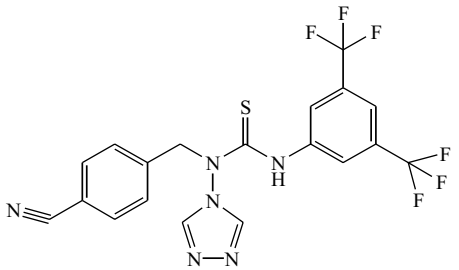
[1,2,4]-Triazole derivatives as antitubercular agent Tuberculosis is an infectious disease that usually affects the lungs, which is caused by bacteria called *Mycobacterium tuberculosis.* Compared with other diseases caused by a single infectious agent, tuberculosis is the second biggest global killer. Tuberculosis can be usually be cured and more than twenty drugs have been developed. But most of the drugs were developed many years ago and some of the drugs have very severe side effects and it is very difficult to take for such a long period of time. Additionally, various human beings are now developed resistant to one or more of the drugs. This is why there is an urgent need of new antitubercular agents. To develop antitubercular agent, Godhani et al. synthesized a series of [1,2,4]-triazole-3-thiones and screened for antitubercular activity against H37Rv strain by using the Lowenstein Jensen slope method. Out of prepared series, four compounds 165a-d shown good antitubercular activity compared to the standard drug isoniazid.



165a-d

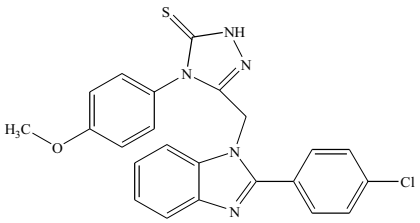
Interestingly, among this series, compounds 165c and 165d with electronegative groups shown potent activity [197].

[1,2,4]-Triazole derivatives as anticancer agent Tokala et al. have been reported the synthesis of a new series of [1,2,4]-triazole-urea/thiourea conjugates and evaluated for their in vitro cytotoxicity against different human cancer cell lines including melanoma mouse cancer cell lines. The results showed that [1,2,4]-triazole-thiourea congeners were found to be potential on MCF-7 cancer cell line. Interestingly, compound 166 with many fluoro groups displayed a broad spectrum of activity against all tested cancer cell lines [198].

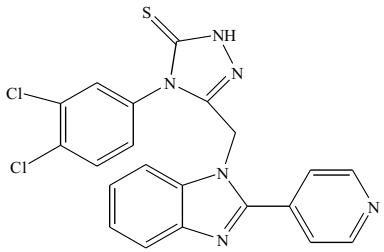


166

[1,2,4]-Triazole derivatives as antioxidant agent Reactive oxygen species and antioxidant have attracted vast attention of researchers because of their implied function in the protection of biological system. A free radical is unstable molecules capable of independent existence that contain one or more unpaired electrons. Free radical damages cells, DNA and collagen and have been implicated in the pathology of more than 50 human diseases. On account of this information, Ayhan-Kilcigil et al. reported the synthesis of some novel benzimidazole derivatives, having [1,2,4]-triazole-3-thione moiety and evaluated for antioxidant activity [199]. The free radical scavenging activity of this series was screened by their ability to bleach the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). In this series, compounds with a chloro group like 5-(2-(p-chlorophenyl)benzimidazol-1-ylmethyl)-4-methoxyphenyl-2,4-dihydro-1,2,4-triazole-3-thione 167 and 5-(2-(4-pyridinyl) benzimidazol-1-ylmethyl)-3,4-dichlorophenyl-2,4-dihydro-1,2,4-triazole-3-thione 168 showed highest interaction with the DPPH radical.

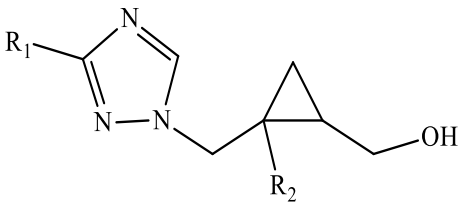


167



168

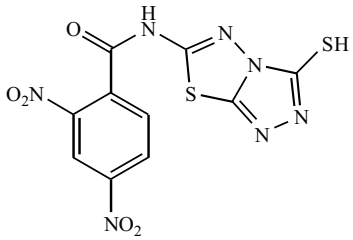
[1,2,4]-Triazole derivatives as antiviral agent Antiviral drugs are a class of medicine precisely used for treating viral infections. Specific antivirals are used for specific viruses [200]. Based on this fact, Benci et al. were able to synthesize [1,2,4]-triazole acyclic cyclopropane nucleoside analogues 169a-d and evaluated for antiviral activity [201].



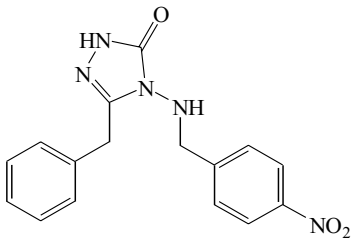
a: R_1=H, R_2=CH_2OH
b: R_1=CH_2OH, R_2=CH_2OH
c: R_1=$CONH_2$, R_2=CH_2OH
d: R_1=$CONH_2$, R_2=$CONH_2$

169a-d

[1,2,4]-Triazole derivatives industrial applications [1,2,4]-Triazole derivatives are also having industrial applications, for instance, some selected triazoles have been used as LED (Electroluminescent devices) [202]. Interestingly, triazole such as 2-mercapto-[1,2,4]-triazole-2,4-dinitro benzamide 170 have been used to increase the efficiency of cooling fluids [203].



170



171

Also, [1,2,4]-triazole derivative 171 have been used as acid–base indicator because it shows reversible, clear color change, sharp and low relative error.

Conclusion

The above literature review demonstrates that heterocylic derivatives are pharmacologically very powerful, and thus, their design and synthesis is the future area of research. Also,the current review strongly described that when one biodynamic heterocyles combined with other biodynamic moiety, the pharmacological activity will be enhanced. In the therapeutic field, there has always been and will continue to be a need for new and novel chemical entities with various pharmacological activities. Our efforts focus on the overview of literature survey of the biological activity of heterocyclic compounds in particular, piperidine, pyridine, quinoline, [1,3,4]-thiadiazole, pyrazole and [1,2,4]-triazole analogues so that many entities will be designed, generated a good pharmocolgical drug in near future.

Acknowledgements Zabiulla thankfully acknowledges the support provided by the Director and management of PG Department, St. Philomena's College (Autonomous), a recognized research center of University of Mysore, Mysore, Karnataka, India. Shaukath Ara Khanum thankfully acknowledges the financial support provided by VGST, Bangalore, under CISEE Programme [Project sanction order: No. VGST/ CISEE /282].

References

1. K.R. Campos, P.J. Coleman, J.C. Alvarez, S.D. Dreher, R.M. Garbaccio, N.K. Terrett, R.D. Tillyer, M.D. Truppo, E.R. Parmee, Science **363**, 6424 (2019)
2. A. Kashyap, N. Adhikari, A. Das, A. Shakya, S.K. Ghosh, U.P. Singh, H.R. Bhat, Curr. Drug Discov. Technol. **15**, 1 (2018)
3. M. Baumann, I.R. Baxendale, J. Organ. Chem. **9**, 2265 (2013)
4. E.M. Carreira, E.T.H. Zurich, Chem. Rev. **115**, 8945 (2015)
5. J.W. Scannell, A. Blanckley, H. Boldon, B. Warrington, Nat. Rev. Drug Discov. **11**, 191 (2012)
6. I.R. Baxendale, J.J. Hayward, S.V. Ley, G.K. Tranmer, ChemMedChem **2**, 768 (2007)
7. M. Hossain, A.K. Nanda, Sci. J. Chem. **6**, 83 (2018)
8. P. Arora, V. Arora, H.S. Lamba, D. Wadhwa, Int. J. Pharm. Sci. Res. **3**, 2947 (2012)
9. T. Omara, B. Musau, S. Kagoya, Am. J. Heterocycl. Chem. **4**, 49 (2018)

10. S.A. Khanum, S. Shashikanth, S.G. Sathyanarayana, S. Lokesh, S.A. Deepak, Pest Manag. Sci. Former. Pest. Sci. **65**, 776 (2009)
11. Zabiulla, A.R. Gulnaz, Y.H.E. Mohammed, S.A. Khanum, Bioorgan. Chem. **92**, 103220 (2019)
12. Zabiulla, M.J.N. Khadri, B.A. Begum, M.K. Sunil, S.A. Khanum, Results Chem. **2**, 100045 (2020)
13. M. Danac, Eur. J. Med. Chem. **74**, 664 (2014)
14. S.G. Kini, A. Bhat, Z. Pan, F.E. Dayan, J. Enzyme Inhib. Med. Chem. **25**, 730 (2010)
15. V.R. Solomon, W. Haq, K. Srivastava, S.K. Puri, S.B. Katti, J. Med. Chem. **50**, 394 (2007)
16. S.I. Pathan, N.S. Chundawat, N.P.S. Chauhan, G.P. Singh, Synth. Commun. **50**, 1251 (2020)
17. M. Zhu, H. Zhou, L. Ma, B. Dong, J. Zhou, G. Zhang, M. Wang, J. Wang, S. Cen, Y. Wang, Eur. J. Med. Chem. **1**, 113450 (2021)
18. R. Paruszewski, M. Strupińska, G. Rostafińska-Suchar, J.P. Stables, Protein Pept. Lett. **10**, 475 (2003)
19. T. Legigan, E. Migianu-Griffoni, M.A. Redouane, A. Descamps, J. Deschamp, O. Gager, M. Monteil, F. Barbault, M. Lecouvey, Eur. J. Med. Chem. **214**, 11324 (2021)
20. M.A.S. Abdelwahid, T. Elsaman, M.S. Mohamed, S.A. Latif, M.M. Mukhtar, M.A. Mohamed, J. Chem. **2019**, 1 (2019)
21. C.M. Zhua, L.R. Konga, Q.L. Shenb, M. Zhanga, J.W. Chena, Q.G. Huanga, L.S. Wanga, Toxicol. Environ. Chem. **65**, 145 (1998)
22. L. He, R. Zhuo, Wuhan Univ. J. Nat. Sci. **3**, 126 (1998)
23. H.D. Gurupadaswamy, P. Thirusangu, B.R.V. Avin, V. Vigneshwaran, M.V.P. Kumar, T.S. Abhishek, V.L. Ranganatha, S.A. Khanum, B.T. Prabhakar, Biomed. Pharmacother. **68**, 791 (2014)
24. C. Labriere, J.H. Andersen, M. Albrigtsen, J.H. Hansen, J. Svenson, Bioorgan. Chem. **84**, 106 (2019)
25. K. Swathi, M. Sarangapani, World J. Pharm. Pharm. Sci. **3**, 2720 (2014)
26. A. Nehad, Abdel-Latif, Sci. Pharm. **74,** 193 (2005)
27. A.S. Lunkad, S.N. Kothawade, K.K. Darkunde, B. Priya, U.R. Bagmar, D.S. Bhandari, Int. J. Chem. Sci. **11**, 1146 (2013)
28. B.L. Wang, H.W. Zhu, Y. Ma, L.X. Xiong, Y.Q. Li, Y. Zhao, J.F. Zhang, Y.W. Chen, S. Zhou, Z.M. Li, J. Agric. Food Chem. **61**, 5483 (2013)
29. M.K. Hosseinnezhad, S. Gharanjig, S. Moradian, Tafaghodi, Arab. J. Chem. **1**, 1 (2015)
30. T. Mori, Chem. Rev. **104**, 4947 (2004)
31. W. Haiss, H.V. Zalinge, H.H. Benreich, D. Bethell, D.J. Schiffrin, S.J. Higgins, R.J. Nichols, Langmuir **20**, 7694 (2004)
32. A.E.A. Wahab, A.A.K. Wasaf, J. Phys. **1032**, 1 (2018)
33. B.A. Begum, N.D. Rekha, B.C.V. Kumar, V.L. Ranganatha, S.A. Khanum, Bioorgan. Med. Chem. Lett. **24**, 3559 (2014)
34. G.W. Nyce, J.A. Lamboy, E.F. Connor, R.M. Waymouth, J.L. Hedrick, Organ. Lett. **4**, 3587 (2002)
35. C. Ramalingan, Y.T. Park, S. Kabilan, Eur. J. Med. Chem. **41**, 683 (2006)
36. K. Lv, Z. Tao, Q. Liu, L. Yang, B. Wang, S. Wu, A. Wang, M. Huang, M. Liu, Y. Lu, Eur. J. Med. Chem. **10**, 151 (2018)
37. M. Al-Ghorbani, N.D. Rekha, V.L. Ranganatha, T. Prashanth, T. Veerabasappagowda, S.A. Khanum, Russ. J. Bioorgan. Chem. **41**, 554 (2015)
38. Hu. De-Jin, S.-F. Liu, T.-H. Huang, Tu. Hai-Yang, A.-D. Zhang, Molecules **14**, 1288 (2009)
39. C. Ding, Y. Pan, X. Yin, C. Tan, Z. Guofu, J. Organ. Chem. **39**, 836 (2019)
40. X. Zhang, P. Lei, T. Sun, X. Jin, X. Yang, Y. Ling, Molecules **22**, 2085 (2017)
41. R.K. Manjusha, S. Begum, A. Begum, K. Bharathi, Asian J. Pharm. Clin. Res. **66**, 73 (2018)
42. D. Ole, Wolthers, Biomed. Res. Int. **1**, 6 (2013)
43. C.R. Ganellin, R.G.W. Spickett, J. Med. Chem. **8**, 619 (1965)
44. P.S. Watson, B. Jiang, B. Scott, Organ. Lett. **2**, 3679 (2000)
45. Zabiulla, V.H. Malojirao, Y.H.E. Mohammed, P. Thirusangu, B.T. Prabhakar, S.A. Khanum, Med. Chem. Res. **28**, 1132 (2019)
46. M.T. Gulluoglu, Y. Erdogdu, S. Yurdakul, J. Mol. Struct. **834**, 540 (2007)
47. Y. Zhou, E. Vlad, K.G. Benjamin, C.A. Geoffrey, Z.W. Sun, D. Murphy, G. Haley, D. Bailey, M. Jamie, F.S. Fish, E. Stephen, T.W. Hermann, D. Wall, Bioorg. Med. Chem. Lett. **17**, 1206 (2007)
48. Q. Zhou, L. Zhang, M. Meng, X. Feng, J. Yang, H. Du, Org. Lett. **18**, 5189 (2016)
49. Z.Y. Liu, Z.H. Wen, X.C. Wang, AngewandteChemie **56**, 5817 (2017)
50. H.P. Singh, S.D. Gupta, N.S.H.N. Moorthy, Int. J. Pharm. Tech. Res. **1**, 282 (2009)
51. Y.Y. Zheng, L. Guo, X.C. Zhen, J.Q. Li, Eur. J. Med. Chem. **54**, 123 (2012)
52. I. Sato, K. Morihira, H. Inami, H. Kubota, T. Morokata, K. Suzuki, N. Hamada, Y. Iura, A. Nitta, T. Imaoka, T. Takahashi, M. Takeuchi, M. Ohtaa, S. Tsukamotoa, Bioorg. Med. Chem. **16**, 144 (2008)
53. Y. Zeng, R. Cao, T. Zhang, S. Li, W. Zhong, Eur. J. Med. Chem. **97**, 19 (2015)
54. S.A. Khanum, V. Girish, S.S. Suparshwa, N.F. Khanum, Bioorgan. Med. Chem. Lett. **19**, 1887 (2009)
55. S. Yang, D. Lu, P. Ouyang, Bioorgan. Med. Chem. Lett. **28**, 1731 (2018)
56. R. Sharma, S. ShubhangiSoman, Eur. J. Med. Chem. **90**, 342 (2015)
57. L. James, V.N.W. Marcus, de Souza, M.S.V. Solange, C.S.W. Maria, Lourenço, J. Mol. Struct. **990**, 67 (2011)
58. L. Kai, Z. Tao, Q. Liu, L. Yang, B. Wang, S. Wu, A. Wang, M. Huang, M. Liu, Y. Lu, Eur. J. Med. Chem. **151**, 1 (2018)
59. J.A. Joule, K. Mills, *Heterocyclic Chemistry*, vol 4 (Oxford, Blackwell, 2000)
60. M. Al-Ghorbani, P. Thirusangu, H.D. Gurupadaswamy, V. Girish, H.G.S. Neralagundi, B.T. Prabhakar, S.A. Khanum, Bioorgan. Chem. **65**, 73 (2016)
61. G. Zeni, R.L. Larock, Chem. Rev. **106**, 4644 (2006)
62. Zabiulla, V. Vigneshwaran, B.A. Begum, G.S. Pavankumar, B.T. Prabhakar, S.A. Khanum, Biomed. Pharm. **95**, 419 (2017)
63. C. Jared, G.L. Robert, A.B. JonathanEllman, J. Am. Chem. Soc. **129**, 5332 (2007)
64. P. Kiuru, J. Yli-Kauhaluoma, in *Heterocycles in Natural Product Synthesis*, ed. by K. Majumdar, S.K. Chattopadhyay (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2011), pp. 267–297. https://doi.org/10.1002/9783527634880.ch8
65. K.E. Bashford, M.B. Burton, S. Cameron, A.L. Cooper, R.D. Hogg, P.D. Kane, D.A. MacManus, C.A. Matrunola, C.J. Moody, A.A.B. Robertson, M.R. Warne, Tetrahedron Lett. **44**, 1627 (2003)
66. J.C. Lewis, R.G. Bergman, J.A.J. Ellman, J. Am. Chem. Soc. **129**, 5332 (2007)
67. C.K. Banerjee, J.D. Umarye, P.R. Kanjilal, Synth. Commun. **43**, 2208 (2013)
68. S.I. Scherbinina, O.V. Fedorov, V.V. Levin, V.A. Kokorekin, M.I. Struchkova, A.D. Dilman, J. Organ. Chem. **82**, 12967 (2017)
69. A.A. Altaf, A. Shahzad, Z. Gul, N. Rasool, A. Badshah, B. Lal, E. Khan, J. Drug Des. Med. Chem. **1**, 1 (2015)
70. G. Sachs, J.M. Shin, C.W. Howden, Aliment. Pharmacol. Ther. **23**, 2 (2006)
71. M.V.D. Almeida, M.V.D.N. Souza, N.R. Barbosa, F.P. Silva, G.W. Amarante, S.H. Cardoso, Lett. Drug Des. Discov. **4**, 149 (2007)
72. M.F. Ansari, D. Idrees, M.I. Hassan, K. Ahmad, F. Avecilla, A. Azam, Eur. J. Med. Chem. **144**, 544 (2018)

73. B. Sun, Y. Dong, K. Lei, J. Wang, L. Zhao, M. Liu, Bioorgan. Med. Chem. **27**, 2427 (2019)
74. B. Jadhav, R. Kenny, Y. Nivid, M. Mandewale, R. Yamgar, Open J. Med. Chem. **6**, 59 (2016)
75. M.S. Sondhi, M. Dinodia, A. Kumar, Bioorgan. Med. Chem. **14**, 4657 (2006)
76. R.C. Elderfield (ed.), *Heterocyclic Compounds*, vol. 6 (Wiley, New York, 1957)
77. M. Shraddha, P.D. Kinjal, P.H. Rajesh, V.N. Shyamali, P.D. Hitesh, Patel, RSC Adv. **4,** 24463 (2014)
78. T. Prashanth, B.R. Vijay Avin, P.Thirusangu, V.L. Ranganatha, B.T. Prabhakar, J.N.N.S. Chandra, S.A. Khanum, Biomed. Pharm. **112,** 108707 (2019)
79. M. Ozyanik, S. Demirci, H. Bektas, N. Demirbas, A. Demirbas, S.A. Karaoglu, Turk. J. Chem. **36**, 233 (2012)
80. P.R. Graves, J.J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A.M. Coley, M. Foley, T.A. Haystead, Mol. Pharmacol. **62**, 1364 (2002)
81. A.T. Vu, S.T. Cohn, E.S. Manas, H.A. Harris, R.E. Mewshaw, Bioorgan. Med. Chem. Lett. **15**, 4520 (2005)
82. Y. Li, X. Shi, N. Xie, Y. Zhao, S. Li, Med. Chem. Commun. **4**, 367 (2013)
83. J. Safari, S.H. Banitaba, S.S. Samiei, J. Chem. Sci. **121**, 481 (2009)
84. M. Qandalee, M. Alikarami, H. Mighani, S. Asghari, S. Beikjani, M. Hatami, Int. Nano Lett. **3**, 49 (2013)
85. B.C. Ranu, A. Hajra, U. Jana, Tetrahedron Lett. **41**, 531 (2000)
86. J. Wu, H.G. Xia, K. Gao, Organ. Biomol. Chem. **4**, 126 (2006)
87. M.A. Zolfgol, P. Salehi, A. Ghaderi, M. Shiri, J. Chin. Biochem. Soc. **54**, 267 (2007)
88. M.H. Sarvari, J. Iran. Chem. Soc. **8**, 119 (2011)
89. M.R. Heravi, Ultrason. Sonochem. **16**, 361 (2009)
90. S. Kumar, S. Bawa, H. Gupta, Mini-Rev. Med. Chem. **9**, 1648 (2009)
91. C. Vittorio, B. Guyen, Y. Opoku-Boahen, J. Mann, S.M. Gowan, M. Lloyd, A.R. Martin, N. Stephen, Bioorgan. Med. Chem. Lett. **10**, 2063 (2000)
92. W. Kemnitzer, J. Kuemmerle, S. Jiang, H.Z. Zhang, N. Sirisoma, S. Kasibhatla, C.C. Grundy, B. Tseng, J. Drewe, X.Z. Cai, Bioorgan. Med. Chem. Lett. **18**, 6259 (2008)
93. J.N. Delgado, W.A. Remers (ed.), *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th edn. (Lippincott-Raven, Philadelphia, PA, 1998). ISBN 0-397-51583-9
94. S.A.A. Mohsen, Korean Chem. Soc. **26**, 719 (2005)
95. L.J. Guo, C.X. Wei, J.H. Jia, L.M. Zhao, Z.S. Quan, Eur. J. Med. Chem. **44**, 954 (2009)
96. Y. Kohno, K. Awano, M. Miyashita, S. Fujimori, K. Kuriyama, Y. Sakoe, S. Kudoh, K. Saito, E. Kojima, Bioorgan. Med. Chem. Lett. **7**, 1515 (1997)
97. Y. Kohno, K. Awano, M. Miyashita, T. Ishizaki, K. Kuriyama, Y. Sakoe, S. Kudoh, K. Saito, E. Kojima, Bioorgan. Med. Chem. Lett. **7**, 1519 (1997)
98. J.M. McCall, R.E. Brink, B.V. Kamdar, L.L. Ska-Letzky, S.C. Perricone, R.C. Piper, Med. Chem. **29**, 133 (1986)
99. I. Sircar, S.J. Haleen, S.E. Burke, H. Barth, J. Med. Chem. **35**, 4442 (1992)
100. A.K. Singh, R. Parthsarthy, J. Kshitiz, G. Mishra, Int. J. Sci. Innov. Discov. **3**, 353 (2011)
101. S. Jalhan, A. Jindal, A. GuptaHemraj, Asian J. Pharm. Clin. Res. **3**, 199 (2012)
102. H. Bhuva, D. Sahu, B.N. Shah, C.M. Dixit, M.B. Patel, Pharmacology **1**, 528 (2011)
103. R. Tripathy, A. Ghose, J. Singh, E.R. Bacon, T.S. Angeles, S.X. Yang, Bioorgan. Med. Chem. Lett. **17**, 1793 (2007)
104. N. Siddiqui, P. Ahuja, W. Ahsan, S.N. Pandeya, S.M. Alam, J. Chem. Pharm. Res. **1**, 19 (2009)
105. N. Foroughifar, A. Mobinikhaledi, S. Ebrahimi, H. Moghanian, B.M.A. Fard, Tetrahedron Lett. **50**, 836 (2009)
106. R.A. Bhat, A.T. Amir, I. Choi, F. Athar, Eur. J. Med. Chem. **46**, 3158 (2011)
107. B.C. Chapleo, M. Myers, P.L. Myers, J.F. Saville, A.C.B. Smith, M.R. Stillingsm, J. Med. Chem. **29**, 2273 (1986)
108. K.Y. Jung, S.K. Kim, Z.G. Gao, A.S. Gross, N. Melman, K.A. Jacobsonb, Bioorgan. Med. Chem. **12**, 613 (2004)
109. H.L. Shen, Y. Li, H.X.H. Shang, S. Tian, Y.S. Lai, L.J. Liu, Chin. Chem. Lett. **24**, 299 (2013)
110. M. Juszczak, J. Matysiak, M. Szeliga, P. Zarowski, N. Niewiadomy, J. Albrecht, Bioorgan. Med. Chem. Lett. **22**, 5466 (2012)
111. A.K. Kumar, V.G. Kumar, N. Renuka, Int. J. ChemTech. Res. **5**, 239 (2013)
112. M.R. Mahendrasinh, H.V. Patel, M.R. Lata, N.K. Patel, Int. J. Pharm. Chem. Biol. Sci. **3**, 814 (2013)
113. C.T. Supuran, A. Scozzafava, Curr. Med. Chem. Immunol. Endocr. Metab. Agents **1**, 61 (2001)
114. Y. Iizawa, K. Okonogi, R. Hayashi, T. Iwahi, T. Yamazaki, A. Imada, Antimicrob. Agents Chemother. **37**, 100 (1993)
115. M. Amir, A. Kumar, I. Ali, S.A. Khan, Indian J. Chem. **48B**, 1288 (2009)
116. S.R. Pattan, B.S. Kittur, B.S. Sastry, S.G. Jadhav, D.K. Thakur, S.A. Madamwar, H.V. Shindhe, Indian J. Chem. **50B**, 615 (2011)
117. N. Linganna, K.M.L. Rai, Synth. Commun. **28**, 4611 (2006)
118. N.C. Desai, A.M. Bhavsar, M.D. Shah, A.K. Saxena, Indian J. Chem. **47**, 579 (2008)
119. K. Arvind, G.S. Mishra, K. Jyoti, J. Appl. Pharm. Sci. **1**, 44 (2011)
120. A. Foroumadi, M. Sorkhi, M.H. Moshafi, M. Safavi, A. Rineh, F. Siavoshi, A. Shafiee, S. Emami, Med. Chem. **5**, 529 (2009)
121. A. Rana, J.M. Alex, M. Chauhan, G. Joshi, R. Kumar, Med. Chem. Res. **24**, 903 (2015)
122. R. Siegel, D. Naishadham, A. Jemal, Cancer J. Clin. **62**, 10 (2012)
123. H.C. Zhao, Y.P. Shi, Y.M. Liu, C.W. Li, L.N. Xua, P. Wang, Bioorgan. Med. Chem. Lett. **23**, 6577 (2013)
124. J.Y. Chou, S.Y. Lai, S.L. Pan, G.M. Jow, J.W. Chern, J.H. Guh, Biochem. Pharmacol. **66**, 115 (2003)
125. G. Shankar, R.A. Kallanagouda, V.A. Pranali, M.S. Sagar, H.C. Dilip, S.D. Amol, Shah, Bioorgan. Med. Chem. Lett. **22,** 917 (2012)
126. U.S. Goksen, N.G. Kelekci, O. Goktas, Y. Koysal, E. Kilic, S. Isik, G. Aktay, M. Ozalp, Bioorgan. Med. Chem. **15**, 5738 (2007)
127. S. Wiebe, N. Jette, Nat. Rev. Neurol. **8**, 669 (2012)
128. C.M. Ulloa, F.G. Gilliam, Nat. Rev. Neurol. **7**, 195 (2011)
129. W.H. Bergstom, R.F. Carzoli, C. Lombroso, D.T. Davidson, W.M. Wallace, Am. J. Dis. Child. **84**, 771 (1952)
130. V.K. Archana, S.A. Kumar, Chem. Biol. Drug Des. **37**, 873 (2002)
131. V.K. Archana, S.A. Kumar, Bioorgan. Med. Chem. **12**, 1257 (2004)
132. K. Tewari, A. Mishra, Bioorgan. Med. Chem. **9**, 7150 (2001)
133. S.L. Janus, A.Z. Magdif, B.P. Erik, N. Claus, Monatsheftefür Chemie-Chem. Month. **130**, 1167 (1999)
134. E.V. Pimerova, E.V. Voronina, Pharm. Chem. J. **35**, 602 (2001)
135. I. Bouabdallah, L.A. Barret, A. Zyad, A. Ramadan, I. Zidane, A. Melhaoui, Nat. Prod. Res. **20**, 1024 (2006)
136. N. Puttaswamy, N.D. Rekha, V.L. Ranganatha, T. Prashanth S.A. Khanum, J. Appl. Pharm. Sci. **8,** 60 (2018)
137. C.K. Chu, J.J. Cutler, J. Hetrocycl. Chem. **23**, 289 (1986)
138. V. Michon, C.H. Du Penhoat, F. Tombret, J.M. Gillardin, F. Lepagez, L. Berthon, Eur. J. Med. Chem. **30**, 147 (1995)
139. M.J. Genin, C. Biles, B.J. Keiser, S.M. Poppe, S.M. Swaney, W.G. Tarpley, Y. Yagi, D.L. Romero, J. Med. Chem. **43**, 1034 (2000)

140. Y.R. Huang, J.A. Katzenellenbogen, Organ. Lett. **2**, 2833 (2000)
141. S.R. Stauffer, C.J. Coletta, R. Tedesco, G. Nishiguchi, K. Carlson, J. Sun, B.S. Katzenellenbogen, J.A. Katzenellenbogen, J. Med. Chem. **43**, 4934 (2000)
142. S. Ruiu, G.A. Pinna, G. Marchese, J.M. Mussinu, P. Saba, S. Tambaro, P. Casti, R. Vargiu, L. Pani, J. Pharmacol. Exp. Ther. **306**, 363 (2003)
143. K. Du, Y. Mei, X.T. Cao, P.F. Zhang, H. Zheng, Int. J. Chem. Eng. Appl. **21**, 238 (2013)
144. L. Knorr, German Patent **26**, 429 (1883)
145. L. Knorr, Ber. Dtsch. Chem. Ges. **16**, 2597 (1883)
146. L. Knorr, A. Blank, Ber. Dtsch. Chem. Ges. **18**, 311 (1885)
147. Y.R. Girish, K.S.S. Kumar, H.S. Manasa, S. Shashikanth, J. Chin. Chem. Soc. **61**, 1175 (2014)
148. S. Ponnala, S.D. Prasad, Synth. Commun. **36**, 2189 (2006)
149. M.E. Braibante, H.T. Braibante, J.K. Da Roza, D.M. Henriques, T.L. de Carvalho, Synthesis **2003**, 1160 (2003)
150. P. Lokhande, K. Hasanzadeh, S.G. Konda, Eur. J. Chem. **2**, 223 (2011)
151. S. Ferfra, N.H. Ahabchane, B. Garrigues, E.M. Essassi, Comptes Rendus de and Académie des Sciences **4**, 905 (2001)
152. S.D. Larsen, T.J. Poel, K.J. Filipski, J.T. Kohrt, J.A. Pfefferkorn, R.J. Sorenson, B.D. Tait, V. Askew, L. Dillon, J.C. Hanselman, G.H. Lu, A. Robertson, C. Sekerke, Kowala, M.C.B.J. Auerbach, Bioorgan. Med. Chem. Lett. **17,** 5567 (2007)
153. M. Ichikawa, M. Ohtsuka, H. Ohki, M. Ota, N. Haginoya, M. Itoh, Y. Shibata, Y. Ishigai, K. Terayama, A. Kanda, K. Sugita, Med. Chem. Lett. **4**, 932 (2013)
154. E. Kick, R. Martin, Y. Xie, B. Flatt, E. Schweiger, T.L. Wang, B. Busch, M. Nyman, X.H. Gu, G. Yan, B. Wagner, M. Nanao, L. Nguyen, T. Stout, A. Plonowski, I. Schulman, J. Ostrowski, T. Kirchgessner, R. Wexler, R. Mohan, Bioorgan. Med. Chem. Lett. **25**, 372 (2015)
155. G.S. Hassan, S.M. Abou-Seri, G. Kamel, M.M. Ali, Eur. J. Med. Chem. **76**, 482 (2016)
156. R.D. Kamble, R.J. Meshram, S.V. Hese, R.A. More, S.S. Kamble, R.N. Gacche, B.S. Dawane, Comput. Biol. Chem. **61**, 86 (2016)
157. J.N. Dominquez, J.E. Charris, M. Caparelli, F. Riggione, Arzneim-Forch, Drug Res. **52**, 482 (2002)
158. E. Akbas, I. Berber, A. Sener, B. Hasanov, Farmaco **60**, 23 (2005)
159. A.M. Vijesh, A.M. Isloor, S. Telkar, S.K. Peethambar, S. Rai, N. Isloor, Eur. J. Med. Chem. **46**, 3531 (2011)
160. J. Wu, Q. Shi, Z. Chen, M. He, L. Jin, D. Hu, Molecules **17**, 5139 (2012)
161. R. Alam, D. Wahi, R. Singh, D. Sinha, V. Tandon, A. Grover, Bioorgan. Chem. **69**, 77 (2016)
162. J.B. Shi, W.J. Tang, R. Li, X.H. Liu, Eur. J. Med. Chem. **90**, 889 (2015)
163. S.A. Galal, A.S. Abdelsamie, S.A. Shouman, Y.M. Attia, H.I. Ali, A. Tabll, R. El-Shenawye, Y.S. El Abd, M.M. Ali, A.E. Mahmoud, Eur. J. Med. Chem. **134**, 392 (2017)
164. B.L. Plassman, K.M. Langa, G.G. Fisher, S.G. Heeringa, D.R. Weir, Neuroepidemiology **29**, 125 (2007)
165. A. Ott, M.M. Breteler, F. van Harskamp, J.J. Claus, T.J. van der Cammen, BMJ **310**, 970 (1995)
166. H.W. Querfurth, F.M. LaFerla, N. Engl. J. Med. **362**, 329 (2010)
167. Y.T. Han, K. Kim, G.I. Choi, H. An, D. Son, H. Kim, H.J. Ha, J.H. Son, S.J. Chung, H.J. Park, Eur. J. Med. Chem. **79**, 128 (2014)
168. A. Hetzhein, K. Mockel, Adv. Heterocycl. Chem. **7**, 183 (1996)
169. J. Sandstrom, Adv. Heterocycl. Chem. **9**, 165 (1968)
170. B. Namratha, L. Santosh, Gaonkar, Int. J. Pharm. Pharm. Sci. **6**, 73 (2014)
171. R.M. Balabin, J. Chem. Phys. **131**, 1 (2009)
172. S.M.H. Al-Majidi, Z.S. Saeed, J. Al-Nahrain Univ. **16**, 59 (2013)
173. D. Prasad, N. Aggarwal, R. Kumar, M. Nath, J. Chem. **51B**, 731 (2012)
174. S.G. Agalave, S.R. Maujan, V.S. Pore, Chem. Asian J. **6**, 2696 (2011)
175. J.K. Sahu, S. Ganguly, A. Kaushik, J. Appl. Pharm. Sci. **4**, 81 (2014)
176. R.G. Lima-Neto, N.N.M. Cavalcante, R.M. Srivastava, F.J.B. Mendonça, A.G. Wanderley, R.P. Neves, J.V.D. Anjos, Molecules **17**, 5882 (2012)
177. C.M. Jamkhandi, J.I. Disouza, J. Pharm. Pharm. Sci. **5**, 249 (2013)
178. V. Patil, W. Guerrant, P.C. Chen, B. Gryder, D.B. Benicewicz, S.I. Khan, B.L. Tekwani, A.K. Oyelere, Med. Chem. **18**, 415 (2010)
179. R.C. Corrales, N.B. de Souza, L.S. Pinheiro, S. Abramo, E.S. Coimbra, A.D. Da Silva, Biomed. Pharmacother. **65**, 198 (2011)
180. O.A. Naif, J. Al-Nahrain Univ. **15**, 1 (2012)
181. Z.A.K. Al-Messri, Um-Salama Sci. J. **6**, 200 (2009)
182. A. Mobinikhaledi, N. Foroughifar, M. Khanpour, S. Ebrahimi, Eur. J. Chem. **1**, 33 (2010)
183. A.M. Al-Azzawi, K.K. Hammud, Iraqi J. Sci. **54**, 782 (2013)
184. A.M.N. Yahya, A.N. MohammadRafidain, J. Sci. **21**, 39 (2010)
185. B.A. Ahmed, S.J. Mohammed, Rafidain. J. Sci. **20**, 11 (2009)
186. H. Yoshioka, H. Sakai, S. Shibayama, *Silver Halide Photographic Photosensitive Material and Production Method Thereof* (Patent Application Publisher, United States, 2013)
187. K. Jawad, Shneine, H. Yusra, Alaraji, Int. J. Sci. Res. **5,** 1411 (2016)
188. G. Pellizari, Gazzetta ChimicaItaliana **41**, 20 (1911)
189. S.K. Younis, Rafidain J. Sci. **22**, 62 (2011)
190. R.H. Udupi, S. Bheemachari, N. Srinivasulu, R. Varnekar, Purushottamachar, Bull. Korean Chem. Soc. **28**, 2235 (2007)
191. D. Li, H. Bao, T. You, Heterocycles **65**, 1957 (2005)
192. S.I. Nagai, T. Ueda, S. Sugiura, A. Nagatsu, N. Murakami, J. Sakakibara, M. Fujita, Y. Hotta, J. Heterocyl. Chem. **35**, 325 (1998)
193. S. Pokuri, R.K. Singla, V.G. Bhat, G.G. Shenoy, Curr. Drug Metab. **15**, 389 (2014)
194. E.M. Flefel, W.A. Tantawy, W.A. El-Sayed, H.H. Sayed, N.M. Fathy, J. Heterocycl. Chem. **2**, 344 (2013)
195. R.S. Keri, S.A. Patil, S. Budagumpi, B.M. Nagaraja, **86,** 410 (2015)
196. S.G. Kucukguzel, P. Cikla-Suzgun, Eur. J. Med. Chem. **97**, 830 (2015)
197. D.R. Godhani, A.A. Jogel, A.M. Sanghani, J.P. Mehta, Indian J. Chem. **54B**, 556 (2015)
198. R. Tokala, S. Bale, I.P. Janrao, A. Vennela, N.P. Kumar, K.R. Senwar, C. Godugu, N. Shankaraiah, Bioorgan. Med. Chem. Lett. **28**, 1919 (2018)
199. G. Ayhan-Kilcigil, C. Kuş, T. Coban, B. Can-Eke, S. Ozbey, M. Iscan, J. Enzyme Inhib. Med. Chem. **20,** 503 (2005)
200. E. Thomas, M.G. Ghany, T.J. Liang, Antivir. Chem. Chemother. **23**, 1 (2012)
201. K. Benci, T. Suhina, L. Mandic, S.K. Pavelic, A.T. Paravic, K. Pavelic, J. Balzarini, K. Wittine, M. Mintas, Antivir. Chem. Chemother. **21**, 221 (2011)
202. K.D. Dobbs, J. Feldman, W.J. Marshall, S.J. McLain, J.S. Meth, G.D. Vo, Y. Wang, J. Phys. Chem. **118**, 27763 (2014)
203. F.A. Hassan, K.W. Younus, Res. J. Biol. Sci. **7**, 48 (2012)