Review Article

A review exploring biological activities of hydrazones

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ABSTRACT

The development of novel compounds, hydrazones has shown that they possess a wide variety of biological activities viz. antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, antimalarial, anticancer, antifungal, antitubercular, antiviral, cardio protective etc., Hydrazones/azomethines/imines possess-NHN = CH- and constitute an important class of compounds for new drug development. A number of researchers have synthesized and evaluated the biological activities of hydrazones. This review aims at highlighting the diverse biological activities of hydrazones.

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Hydrazones, related to ketones and aldehydes belong to a class of organic compounds with the structure, $R_1R_2C = NNH_2$.[1] These compounds possess diverse biological and pharmacological properties such as antimicrobial, anti-inflammatory, analgesic, antifungal, anti-tubercular, antiviral, anticancer, antiplatelet, antimalarial, anticonvulsant, cardio protective, antihelmintic, antiprotozoal,[2] anti-trypanosomal,[3] antischistosomiasis etc.[4] These compounds contain C = N bond, which is conjugated with a lone pair of electrons of the functional nitrogen atom.[5] The nitrogen atoms of the hydrazones are nucleophilic and the carbon atom has both electrophilic and nucleophilic nature.[6] The α-hydrogen of hydrazones is more potent than that of acidic ketones.[7] The combination of hydrazones with other functional group leads to compounds with unique physical and chemical character.[8] Owing to their biological and pharmacological properties, they are considered important for the synthesis of heterocyclic compounds.[9]

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BIOLOGICAL ACTIVITY

Antimicrobial activity

The emerging bacterial resistance causes a widespread problem for the treatment of various infections. Therefore, the search for antimicrobials is a never-ending task. Now-a-days a number of hydrazone derivatives have been developed and evaluated for their antibacterial activity. Aslan *et al.*,[10] investigated the antibacterial activity of sulfonyl derivatives (1). Certain steroidal hydrazines (2, 3) have been synthesized by Khan[11] which possess *in-vitro* antibacterial activity. Hydrazones bearing imidazoles (4) have been synthesized and screened for antibacterial activity against numerous bacterial strains by Abdel-Wahab *et al.*[12] Palekar *et al.*,[13] synthesized different thiazolidinone derivatives (5, 6) using hydrazine hydrate and evaluated them for their *in-vitro* antibacterial activity. Wang *et al.*,[14] synthesized hydrazone derivatives (7) with significant antibacterial activity. Hydrazone derivatives containing transition metal complex (8) were synthesized and evaluated for antimicrobial activity by Babahan *et al.*[15] Ozkay *et al.*,[16] synthesized novel benzimidazole derivatives bearing hydrazone moiety (9) with antibacterial activity against different bacterial strains. Khalil *et al.*,[17] synthesized hydrazone derivatives (10) and reported them as potential antibacterial agent. Hydrazone derivatives (11) synthesized by Abdel-Aziz and Mekawey[18] exhibited antibacterial activity with minimum inhibitory concentration (MIC) of 75 μg/mL. Good antibacterial activity

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of hydrazone derivatives (12) was reported by Bawa *et al.*[19] Hydrazone derivatives (13), synthesized by Sharma *et al.*,[20] exhibited antibacterial activity against various bacterial strains. Antibacterial activity of certain hydrazone derivatives (14) was reported by Kendall *et al.*[21] Jubie *et al.*[22] synthesized hydrazone derivatives (15, 16) and reported them as promising antibacterial agents. Govindasami *et al.*[23] synthesized and evaluated vanillin related hydrazone derivatives for their antibacterial activity. Compounds 17 and 18 exhibited good activity.

Tuberculosis is a chronic, infectious and most prevalent disease all over the world. It is caused by different strains of the *Mycobacterium tuberculosis*. Lungs, liver and bones are most susceptible to infection. The activity of the newer agents is mostly tested against virulent H37Rv strain. Kamal *et al.*,[24] synthesized nitroheterocyclic based 1,2,4-benzothiadizines (19), which exhibited MIC of 1 μg/mL. Raja *et al.*,[25] synthesized hydrazone derivatives (20) and reported to have MIC of 6.25 μg/mL. Telvekar *et al.*,[26] developed benzofuran-3-carbohydrazide derivatives (21) with good anti-tubercular activity. Hydrazone derivatives (22) synthesized by Gemma *et al.*,[27] exhibited MIC of 6.25 μg/mL. Mahajan *et al.*,[28] synthesized ferrocene-based hydrazone derivatives (23) with significant antitubercular activity. 1*H*-indole-2,3-dione based hydrazones (24), synthesized by Karali *et al.*,[29] exhibited half maximal inhibitory concentration (IC_{50}) of 7.6 μg/mL. Hydrazones (25), synthesized by Eswaran *et al.*,[30] exhibited a MIC of 6.25 μg/mL. Hydrazones (26, 27) synthesized by Imramovský *et al.*,[31] based on isonicotinoylhydrazide, pyrazinamide, p-aminosalicylic acid, ethambutol, and ciprofloxacin exhibited MIC of 0.78 μg/mL and 3.13 μg/mL respectively. Hearn *et al.*,[32] synthesized anti-tubercular agents (28, 29) which showed MIC of 0.06 μg/mL and 0.20 μg/mL respectively. Nayyar and Jain[33] synthesized disubstituted quinolone based hydrazides (30, 31) with good activity profiles. Turan-Zitouni *et al.*,[34] synthesized thiazolyl hydrazones (32) having anti-tubercular activity with MIC of 2.5 μg/mL. 4-(adamantan-1-yl)-2-substituted quinoline based hydrazones (33) synthesized by Nayyar *et al.*,[35] showed MIC of 1.00 μg/mL. Imramovský *et al.*,[31] synthesized isonicotinyl derivatives (34) with a MIC of 3.13 μg/mL.

Fungal infections are generally observed as superficial or systemic infections in humans, animals as well as plants. The development of antifungal agents has surpassed the development of antibacterials. Secci *et al.*,[36] developed novel Hydrazine derivative (35) and evaluated for *in-vitro* anti-*Candidal* activity which exhibited MIC of 0.25 μg/mL. Novel hydrazine thiazole derivatives (36) have been synthesized by Maillard *et al.*,[37] and reported to exhibit anti-*Candidal* activity with MIC of 0.25 μg/mL. Altintop *et al.*,[38] developed, evaluated novel hydrazone derivatives (37) for *in-vitro* anti-*Candidal* activity, and reported to have MIC of 0.05 μg/mL. Hydrazide derivatives (38) synthesized by Telvekar *et al.*,[26] exhibited MIC of <15.62 μg/mL. Chimenti *et al.*[39] synthesized 2-thiazolylhydrazones (39) and reported to have potential activity against various strains of *Candida* species. Kocyigit-Kaymakcioglu *et al.* synthesized and evaluated the antifungal activity of various 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles. Out of these, 4-Fluorobenzoic acid ([5-bromothiophen-2-yl] methylene) hydrazide (40) exhibited highest inhibitory activity against *Candida albicans*, with MIC value of 125 μg/mL.[40]

Virus is a small infectious agent, which can replicate only inside the living cell of an organism. It infects all types of organisms-humans, animals as well as plants. El-Sabbagh and Rady[41] evaluated the antiviral activity of hydrazone derivatives (41) against hepatitis A virus. Tian *et al.*,[42] synthesized hydrazone derivatives (42, 43) as potential targets of human immunodeficiency virus-1 capsid protein. The half maximal effective concentration (EC_{50}) value of the agents was reported to be 0.21 and 0.17 μM respectively [Figure 1].

Analgesic and anti-inflammatory activity

A number of hydrazone derivatives have been developed to overcome gastrointestinal disturbance and toxicity. Mohamed Eissa *et al.*,[43] developed anthranilic acid derivatives (44) and reported to have significant anti-inflammatory activity. Hydrazones containing 5-methyl-2 benzoxazolinones (45), developed by Salgin-Gökşen *et al.*,[44] were reported to exhibit good analgesic and anti-inflammatory activity. Khan *et al.*,[45] have described the anti-inflammatory activity of hydrazones derivatives of quinoxalinone (46). Rajitha *et al.*,[46] have reported good anti-inflammatory activity of aryl hydrazone derivatives (47). Benzylidene hydrazides (48) with prominent analgesic and anti-inflammatory activity, exhibiting percentage inhibition of 68.66 have been synthesized by Bhandari *et al.*[47] Gökçe *et al.*,[48] reported the analgesic and anti-inflammatory activity of 6-substituted-3 (2*H*)-pyridazinone-2-acetyl-2-(*p*-substituted benzal) hydrazone derivatives (49). Moldovan *et al.*,[49] synthesized various hydrazone derivatives (50) with promising *in-vivo* anti-inflammatory activity. Kümmerle *et al.*,[50] developed N-acylhydrazone derivatives (51, 52) with ED_{50} value of 2.3 and 1.6 mg/kg respectively [Figure 2].

Anticancer activity

World Health Organization defines cancer as the rapid creation of abnormal cells that grow beyond their usual boundaries and which can invade adjoining parts of the body and spread to other organs. Dandawate *et al.*,[51] developed plumbagin hydrazone derivatives (53) with high activity against breast cancer. Mohareb and Al-Omran[52] synthesized cyanoacetyl hydrazone with pregnanolone derivatives (54) active against multiple cancer cell lines. Aydın *et al.*,[53] synthesized and evaluated flurbiprofen hydrazide derivatives (55) against ovarian and leukemia cancer cell lines. Cui *et al.*,[54] synthesized acylhydrazones (56) and reported to have potent activity against the human promyelocytic leukemic cells (Hl-60). Al-Said *et al.*,[55] synthesized certain compounds (57) and reported to have *in-vitro* anticancer activity against human breast cancer cell lines MCF7. Liu *et al.*,[56] synthesized, evaluated acetyl hydrazone derivatives (58) for antitumor activity against A549, HCT11b, HepG2, PC-9 and A375 cell lines with an IC_{50} value of 4-17 μM. Aryl hydrazone derivatives (59) synthesized by Vogel *et al.*,[57] were reported to have an IC_{50} of 6.7 nM against MDA-MB 231 and MCF-7 breast cancer cell lines. Xu *et al.*,[58] screened

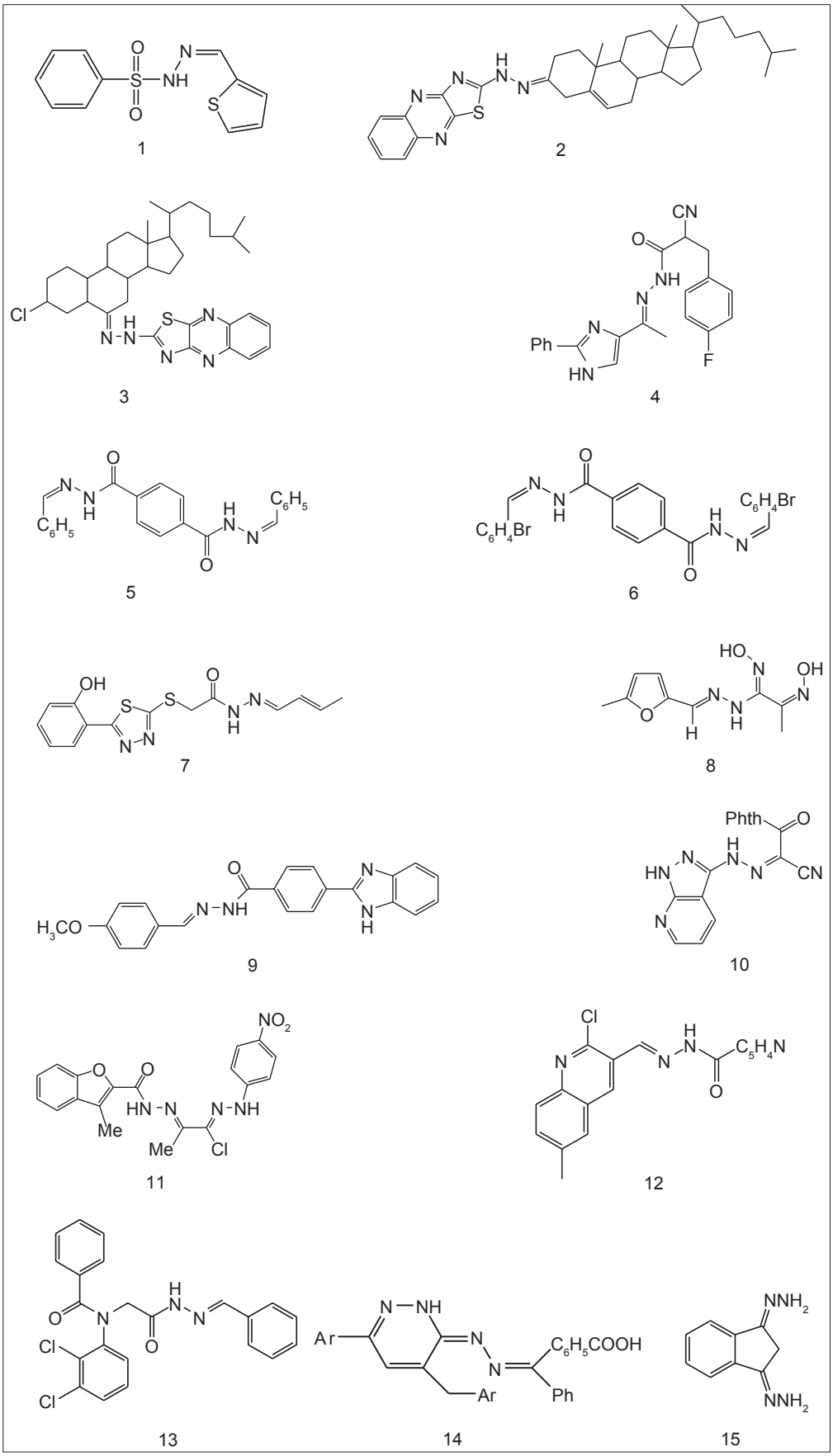
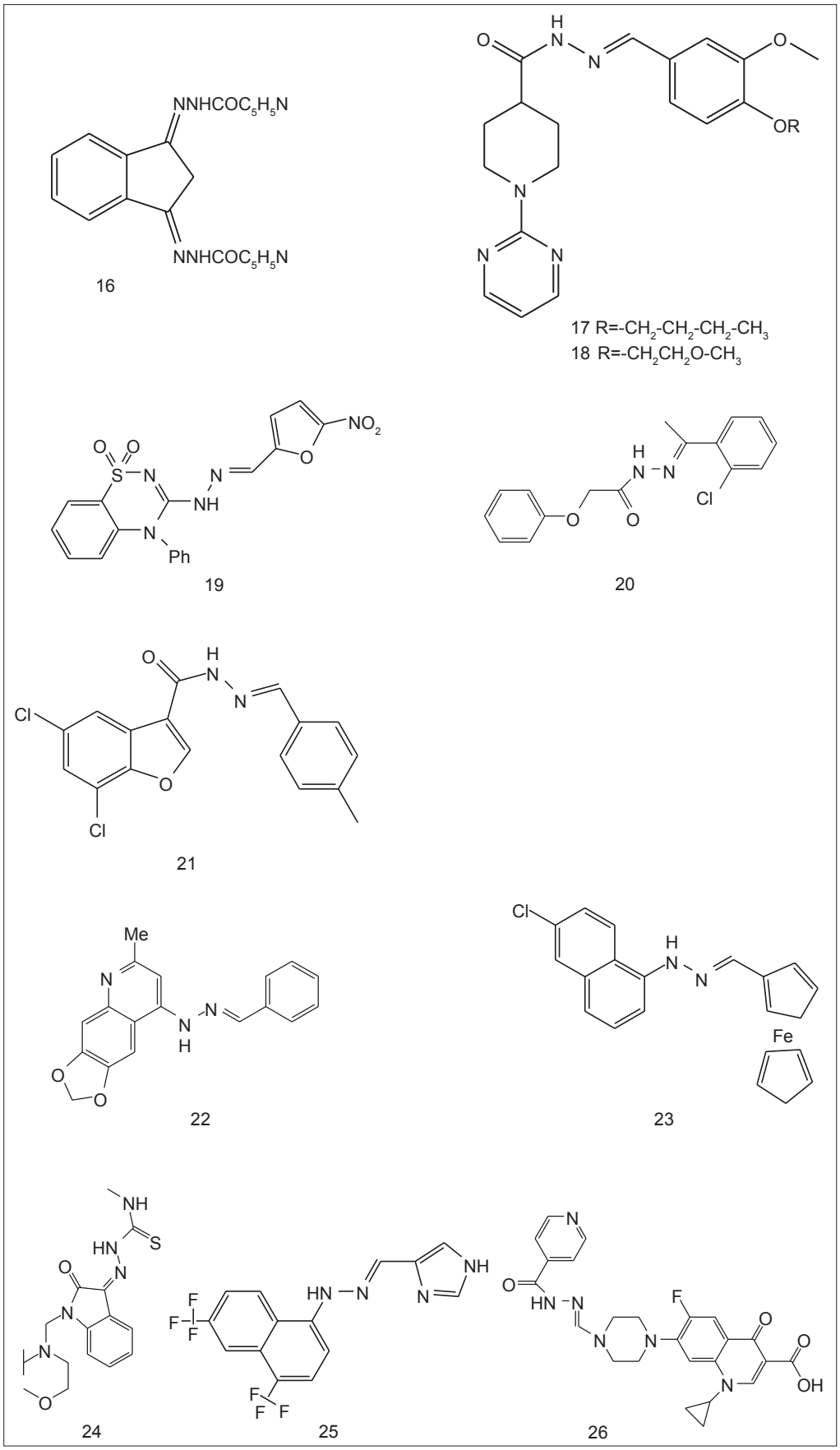


Figure 1: Structure of hydrazones reported as antimicrobial agents (Contd...)



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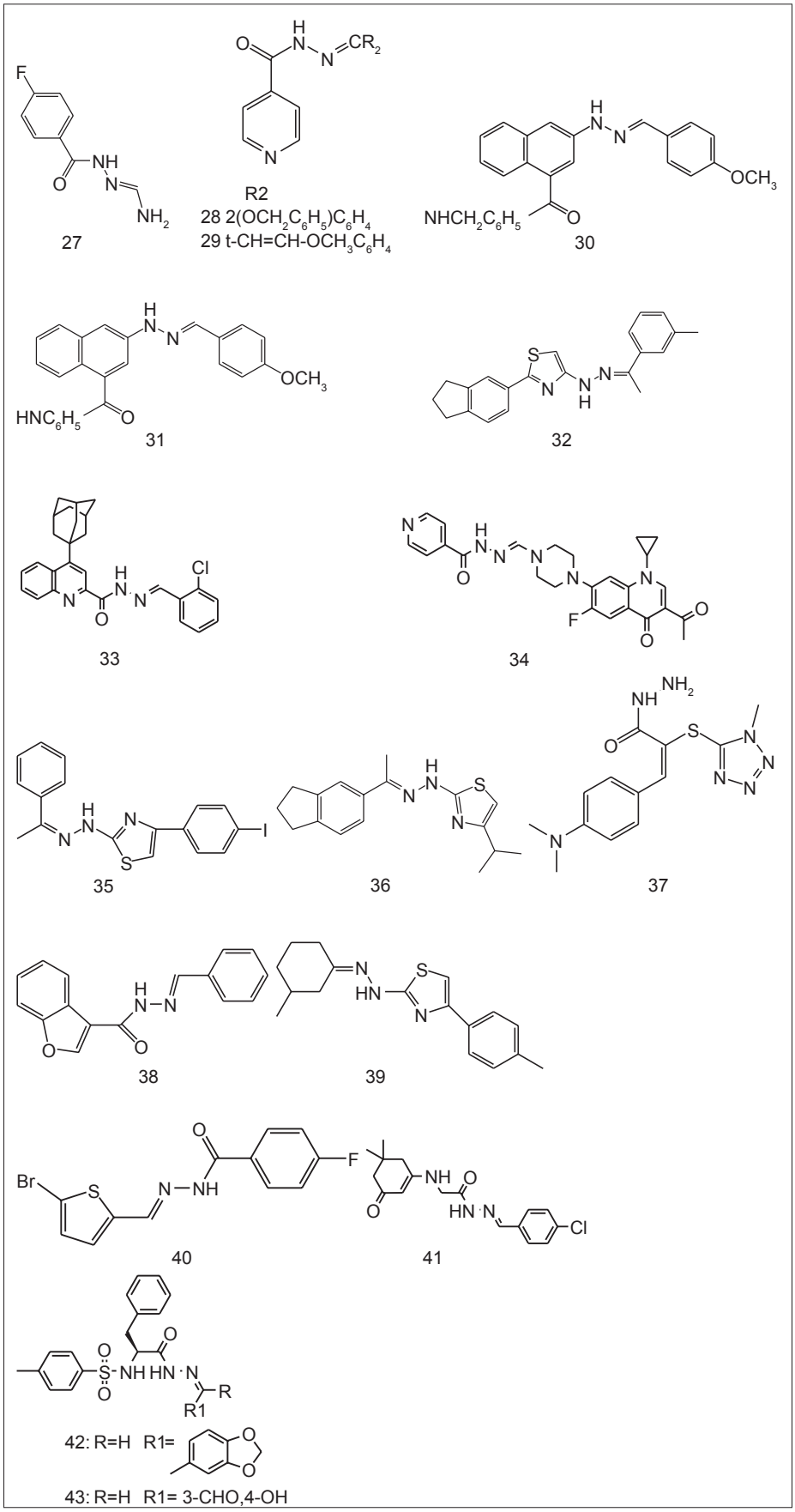

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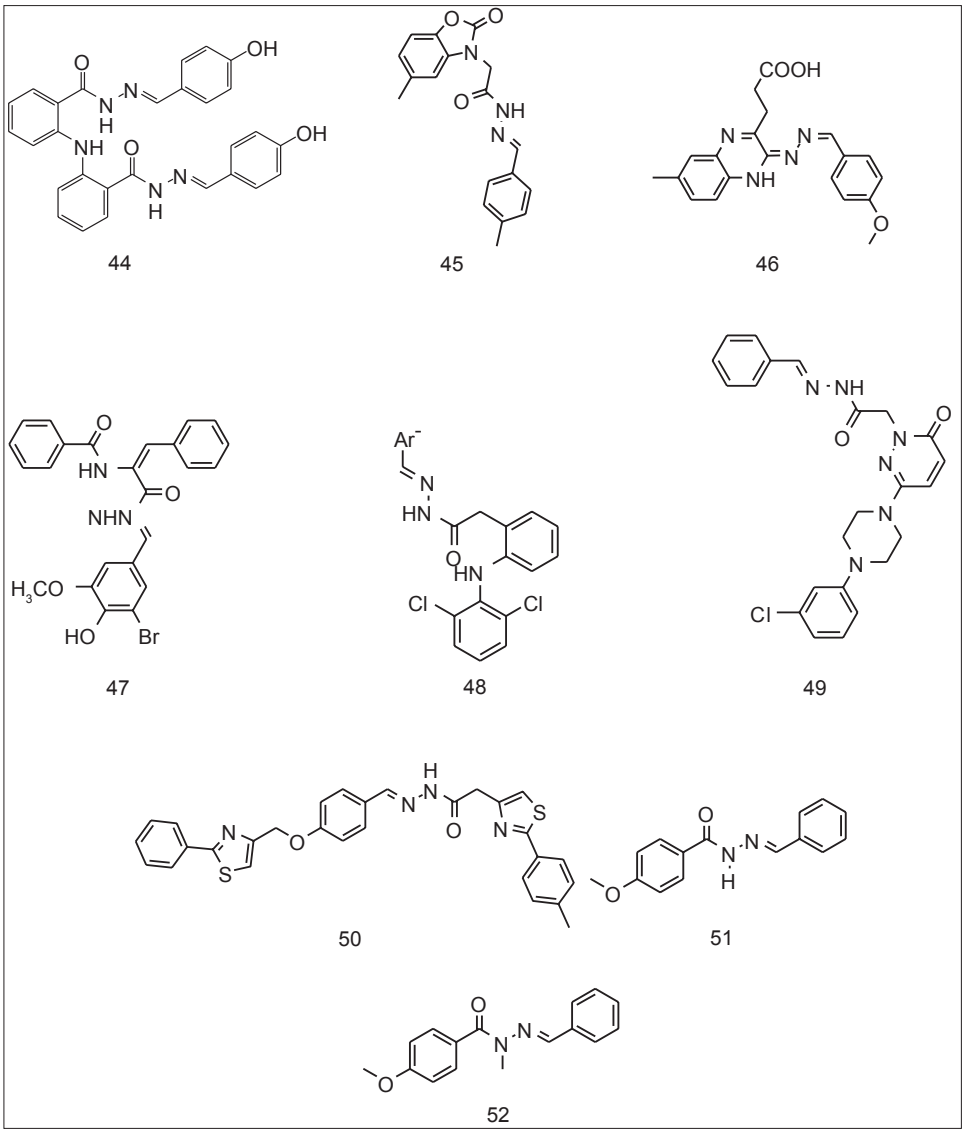


Figure 2: Structure of hydrazones reported as analgesic and anti-inflammatory agents

hydrazone derivatives (60) for kinase inhibition in different cell lines. Benites *et al.*,[59] synthesized hydrazone derivatives (61) and reported them to have significant antiproliferative activity. Hydrazone derivatives reported by Hayakawa *et al.*,[60] (62, 63, 64) exhibited marked PI3 kinase p110 α inhibition. Zheng *et al.*,[61] synthesized hydrazone derivatives (65) with the propensity to act against A549 lung cancer cell lines. Xia *et al.*,[62] synthesized various hydrazones (66) with IC_{50} value of 3.33 μM against A549 lung cancer cell lines. Gürsoy *et al.*,[63] reported the anticancer activity of thiazolohydrazides (67) against prostate cancer. Despaigne *et al.*,[64] have described acetylpyridine and benzoylpyridine derived hydrazones (68, 69) as agents against brain tumor [Figure 3].

Central nervous system (CNS) activity

CNS diseases can affect either brain or the spinal cord resulting in psychological and neurological disorder. Hydrazones are reported to have activity against various disorders of CNS. Salgin-Gökşen *et al.*,[65] synthesized benzylidene hydrazone derivatives (70) and screened them for *in-vitro* monoamine oxidase inhibitory (MAO-B) activity for Parkinson's disease. Novel 2-Methoxy acyl hydrazone derivatives (71) synthesized by Cutshall *et al.*,[66] were evaluated for inhibition of phosphodiasterase 10A (PDE10A), a PDE responsible for neurological and psychological disorders like schizophrenia. Certain anticonvulsant bishydrazones (72) and hydrazones (73) were developed by Kulandasamy *et al.*[67] de Oliveira *et al.*,[68] synthesized and evaluated the antidepressant activity of hydrazones (74). Gökhan-Kelekçi *et al.*,[69] synthesized hydrazone derivatives (75, 76), reported their selective MAO-B inhibition and hence useful in the treatment of depression [Figure 4].

Antiprotozoal activity

Protozoa are a diverse group of unicellular eukaryotic organisms affecting human beings, especially in tropical countries. Aryl hydrazone derivatives (77) synthesized by Siddiqui *et al.*,[70]

have been evaluated against HM1: IMSS strain of *Entamoebica histolytica* for anti-amoebic activity and reported to have IC_{50} 0.13 μM. Gerpe *et al.*,[71] described the anti-*Trypanosomal* activity of 5-nitrofuran hydrazones (78). Caputto *et al.*,[72] synthesized hydrazine derivatives (79) and reported to have activity against *Trypanosoma cruzi (T. cruzi)*. Carvalho *et al.*,[73] synthesized Cinamic N-acyl hydrazones (80) with good anti-*Trypanosomal* activity. dos Santos Filho *et al.*,[74] synthesized hydrazone derivatives (81, 82) against *T. cruzi*. Trypanosomicidal activity of hydrazones (83, 84) has been reported by Porcal *et al.*[75] Hydrazone derivatives (85) developed by de Aquino *et al.*,[76] have been reported to be useful in infections caused by *Toxoplasma gondii*. Caputto *et al.*,[77] reported the inhibitory activity of hydrazones (86, 87) against cruzipain-a major cysteine protease of *T. cruzi*.

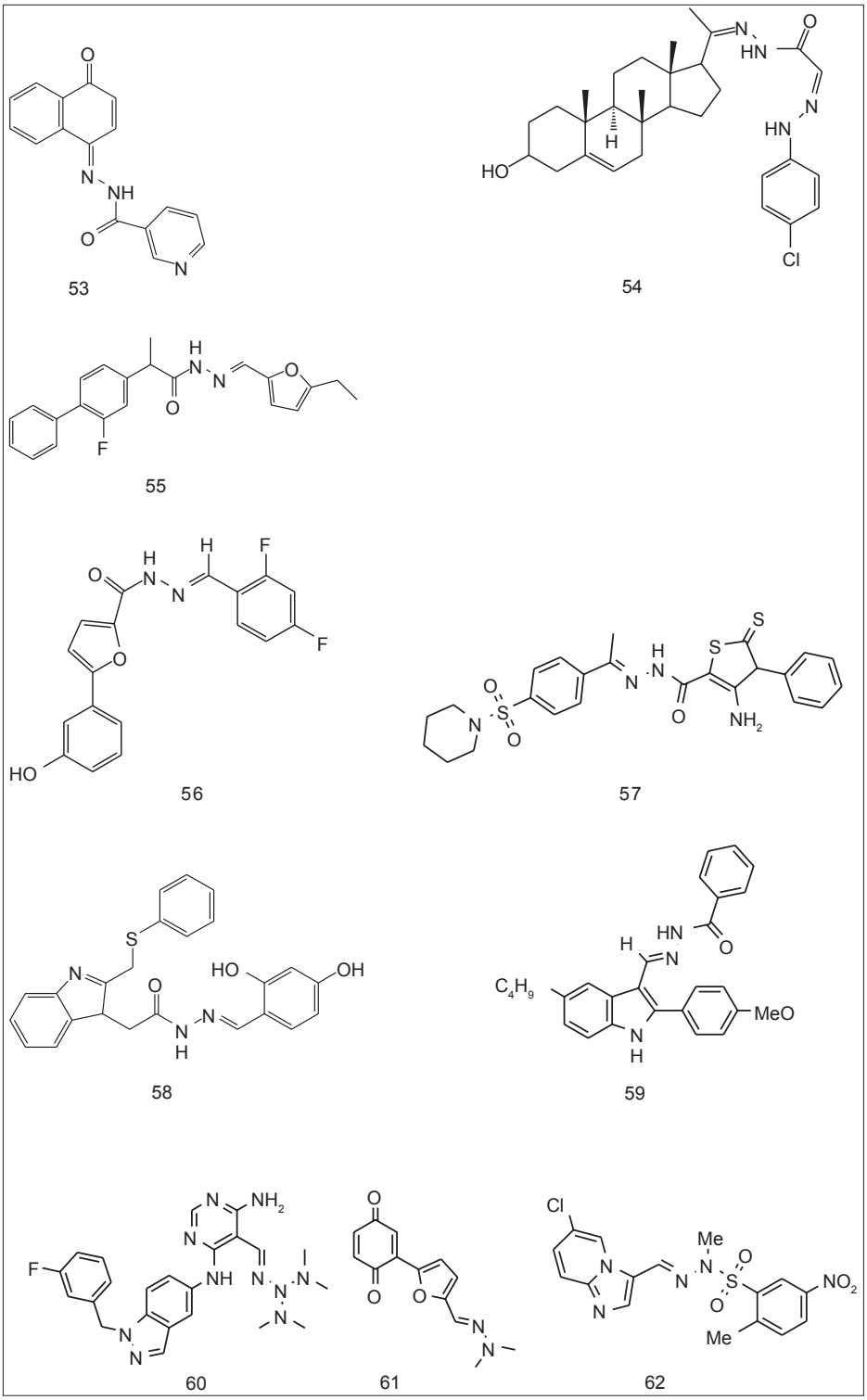
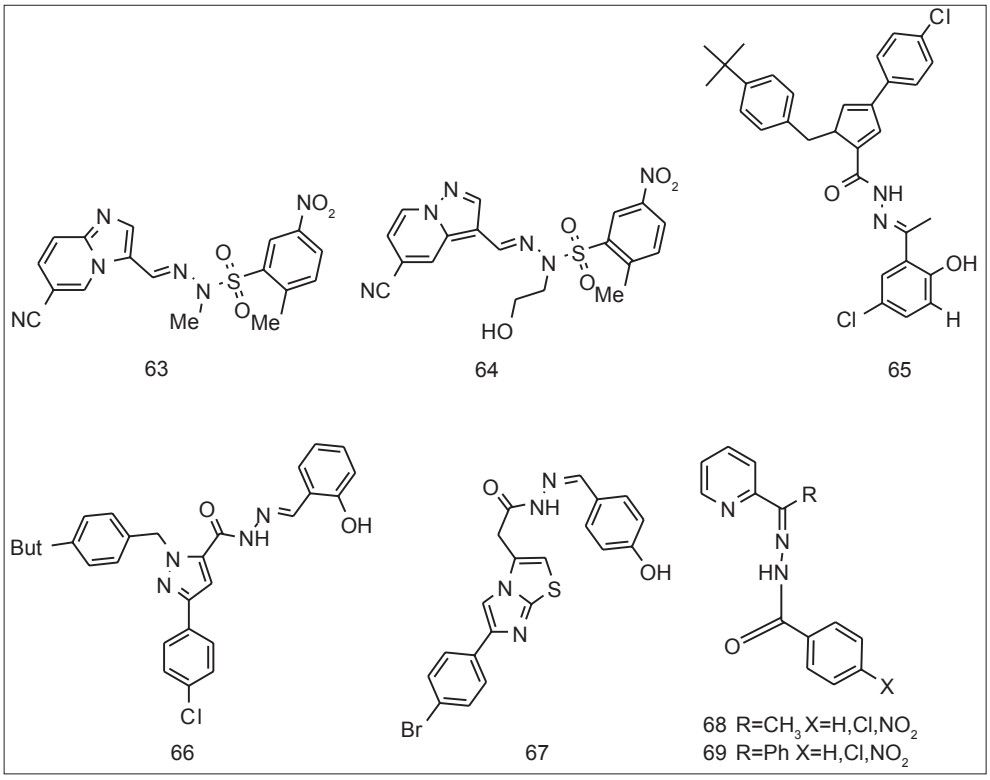


Figure 3: Structure of hydrazones reported as anticancer agents (Contd...)



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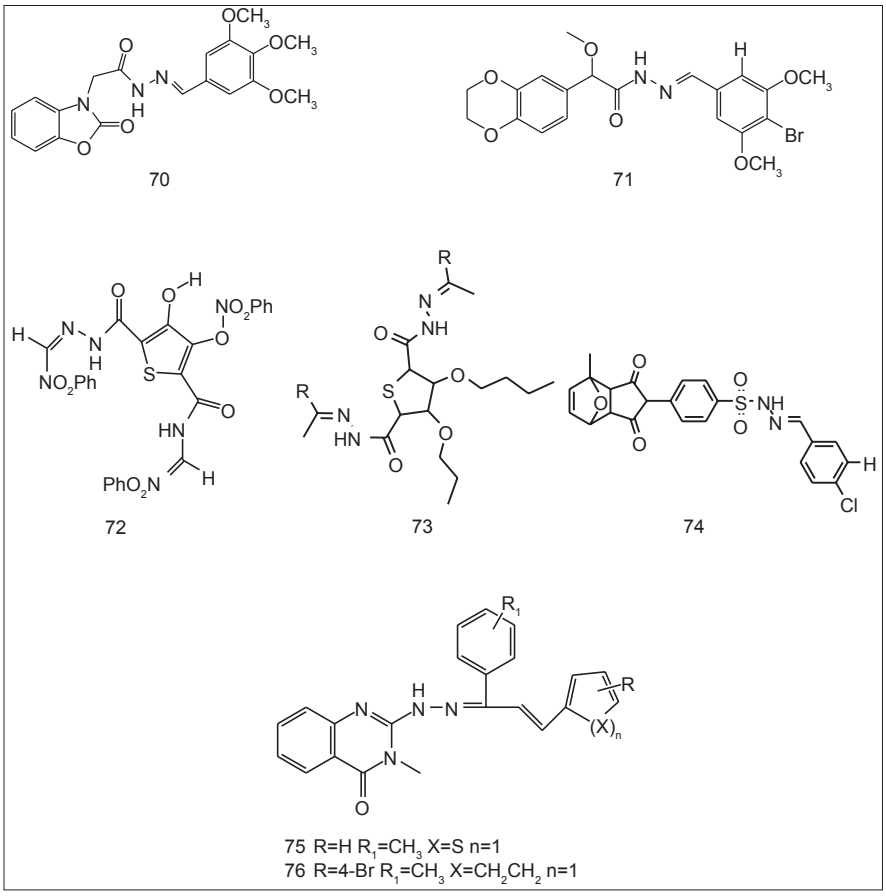

Figure 4: Structure of hydrazones reported as CNS agents

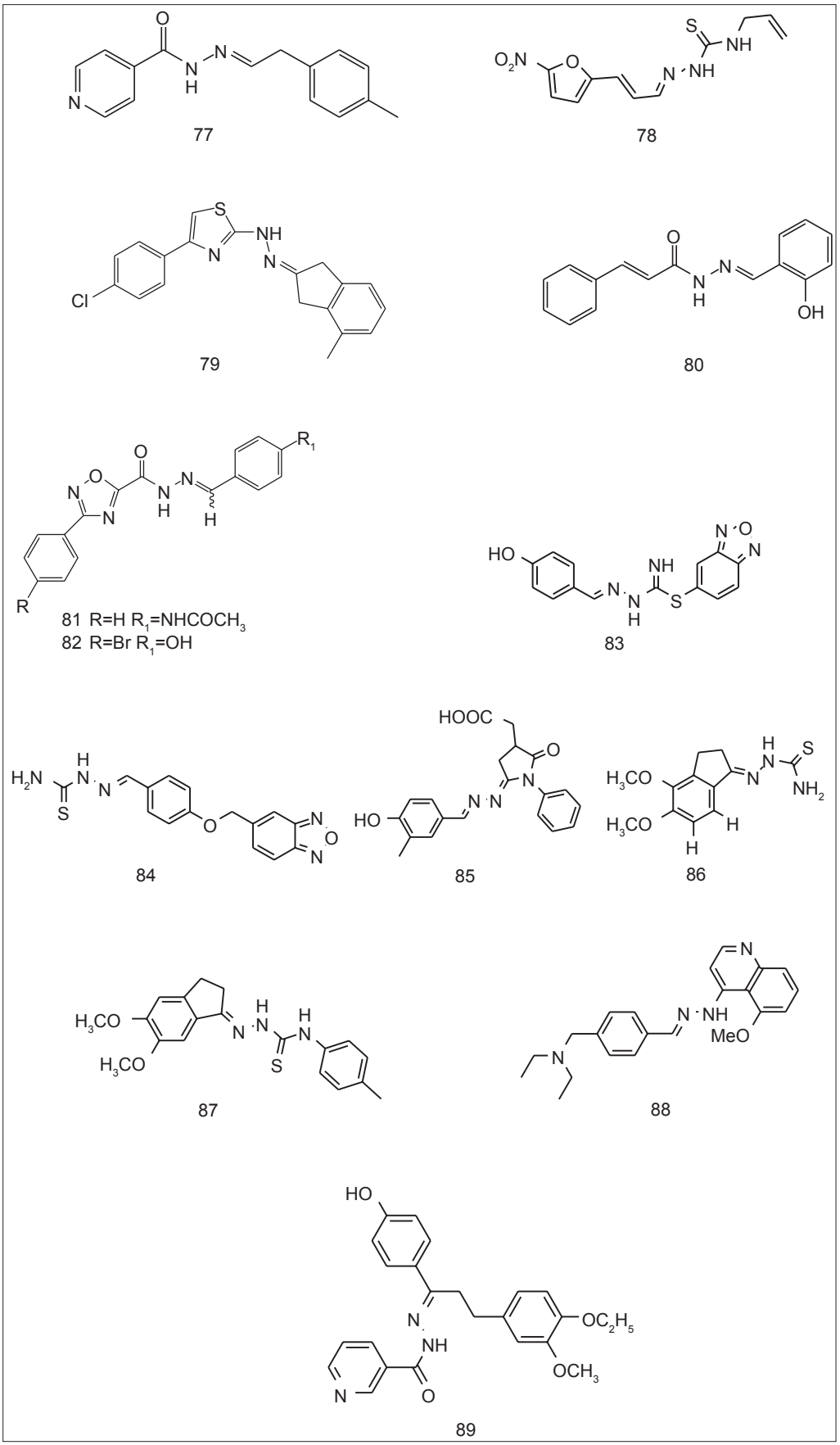

Figure 5: Structure of hydrazones reported as antiprotozoal agents

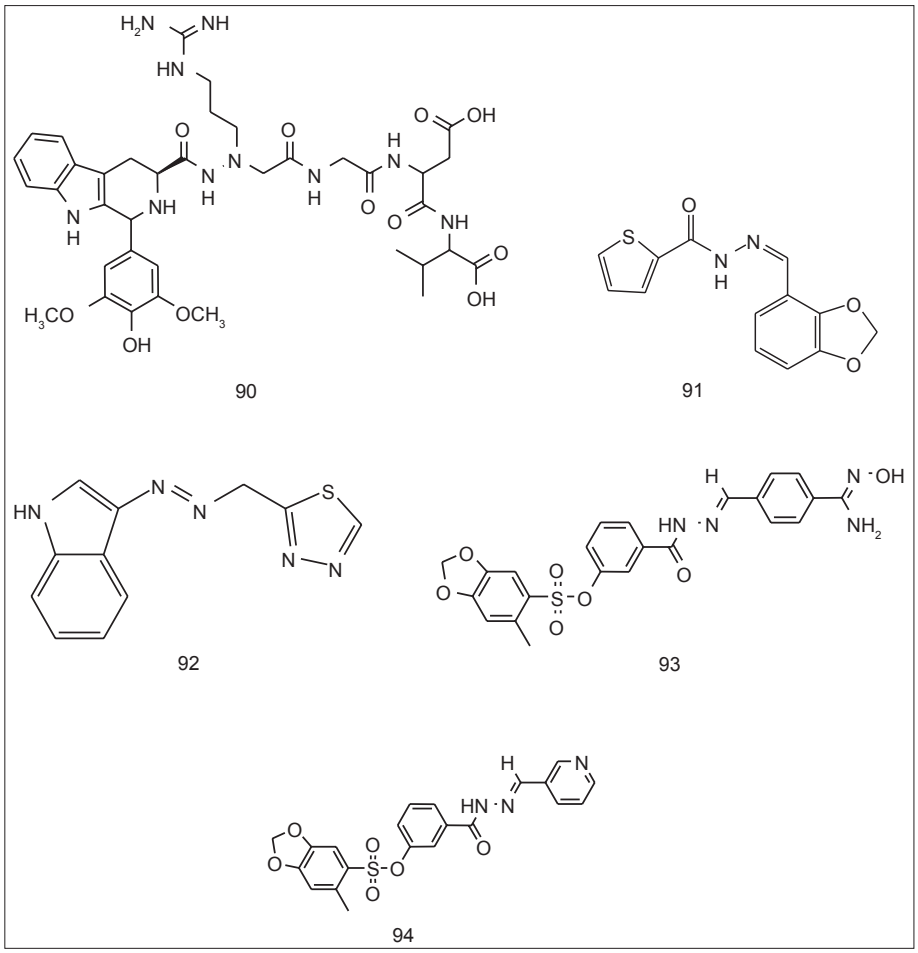

Figure 6: Structure of hydrazones reported as cardioprotective and antiplatelet agents

Malaria is a widespread infectious disease specifically of the tropics caused by *Plasmodium*. Antimalarial propensity of hydrazines (88) has been reported by Fattorusso *et al.*[78] against D10, W2 and 3D7 plasmodial strains with an IC_{50} value of 39.2, 79.0 and 11.0 nM respectively. Acharya *et al.*,[79] synthesized hydrazide derivatives (89) with an IC_{50} of 160 nM/mL as against 280 nM/mL of the reference chloroquine [Figure 5].

Cardio protective activity

Cardiovascular disease is a class of diseases that involve the heart and blood vessels. Despite the extensive research, it still remains the major cause of mortalities world-wide. Bi *et al.*,[80] reported hydrazone derivatives (90) to have potent activity against ischemia-reperfusion induced cardiac infarct size. Leal, *et al.*,[81] synthesized acylhydrazone derivative (91) and reported to have high anti-hypertensive activity.

Antiplatelet activity

Antiplatelet drugs are the agents which decrease platelet aggregation and inhibit thrombus formation. Mashayekhi *et al.*,[82] demonstrated the antiplatelet activity of hydrazone derivatives (92) containing indole moiety. Hydrazone derivatives (93, 94) synthesized by Lima *et al.*,[83] were reported to inhibit platelet aggregation induced by collagen and thrombin [Figure 6].

CONCLUSION

The present review highlights the use of hydrazones as lead for the development of newer compounds. Biological activities of hydrazones include antibacterial, anticonvulsant, analgesic, anti-inflammatory, cardio protective, antiplatelet, anticancer etc., With proper designing, synthesis and structure activity relationship, a number of compounds can be developed with diverse biological activities.

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