Research Progress on Biological Activities of N-Acylhydrazones in Recent Five Years

Xiaoyan Shen, Yang Wang, Kaiyue Yin, Jiwen Sheng*

Weifang Medical University, Weifang, Shandong, 261053, China.

Abstract

N-Acylhydrazones are a class of organic compounds with the general structure R_1-CO-NR_2-N=CR_3R_4. N-Acylhydrazones are important structural motifs in drug design and medicinal chemistry due to their reported biological activities. Acylhydrazone compounds proved to have antibacterial, antifungal, antiviral, anticancer, anti-angiogenesis, anti-inflammatory, analgesic, anti-central system disorder, antimalarial, trypanocidal, anti-leishmanial, antithrombotic and antioxidant biological activities. This paper reviews the biological activities of acylhydrazone compounds in recent five years, in order to promote their potential applications in the pharmaceutical research and development.

Keywords

N-Acylhydrazone, Biological activity, Pharmaceutical research and development.

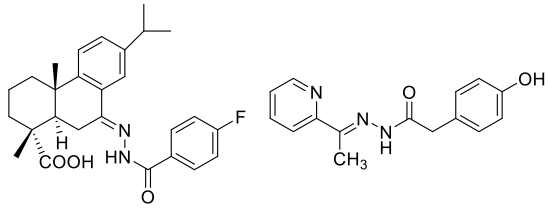
1. Introduction

N-acylhydrazone compounds are the products obtained by condensation of hydrazides with aldehydes or ketones, and a class of Schiff base compounds are obtained after modification of hydrazine compounds. *N*-acylhydrazones have attracted wide attention because of their ease of synthesis and diverse biological activities [1]. Acylhydrazone group is one of the most common functional groups in medicinal chemistry, has been in a large role in a variety of molecular targets hit and lead compounds were identified [2]. Many acylhydrazone compounds have been synthesized and evaluated their various biological activities. In this review, we focus on biological activities of acylhydrazone compounds reported in recent five years.

2. Biological Activities

2.1 Antimicrobial activity

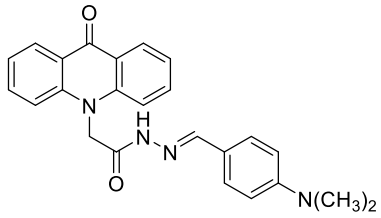
Despite the availability of a variety of antimicrobials, bacterial resistance and the re-emergence of disease-causing bacteria remain a serious medical problem. The identification of new, safer and selective antimicrobials is a major interest in pharmacochemical research. Recently, Zhi Zhou *et al*. showed that C-7 acylhydrazone derivatives of dehydroabietic acid had inhibitory effects on *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. Compound 1 showed the strongest inhibitory activity against *Staphylococcus aureus* and *Bacillus subtilis*, the diameters of bacteriostatic rings reaching 1.68 and 1.45 cm, respectively [3]. 2-acetylpyridine-4-hydroxy phenylacetyl acylhydrazone (2) inhibited the growth of *Staphylococcus aureus* and *Bacillus subtilis* with MIC values of 200 μg/mL and 150 μg/mL, respectively [4]. Tow novel water-soluble isatin-3-acylhydrazones 3 and 4 had strong inhibitory effects on *Staphylococcus aureus* and *Bacillus cereus* with MIC 12.6 *μM*, providing necessary conditions for further synthesis and search for new isatin based antibacterial substances [5].



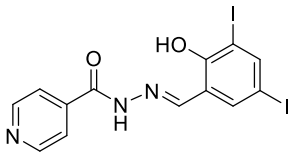
1 2 3 4

Mohammed Aarjane *et al*. [6] synthesized novel *N*-acylhydrazone derivatives from acridone, and MIC results showed that compound 5 had high antibacterial activity against *Pseudomonas putida* with MIC = 38.46 μg/mL.

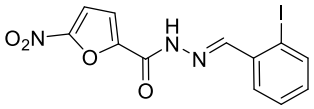
Łukasz Popiołek *et al*. have synthesized a strong resistance of Gram-positive bacteria acylhydrazone of isonicotinic acid (6), which indicated also good antifungal effect towards *Candida* spp[7]. Acylhydrazone of 5-nitrofuran-2-carboxylic acid (7) showed high antibacterial activity, especially against Gram-positive bacteria. Moreover, compound 7 had particularly antifungal effect to *Candida* spp [8].



5

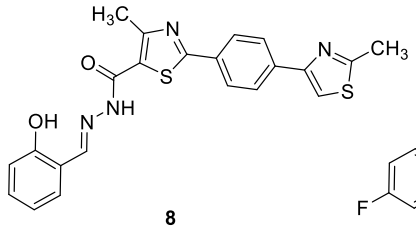


6

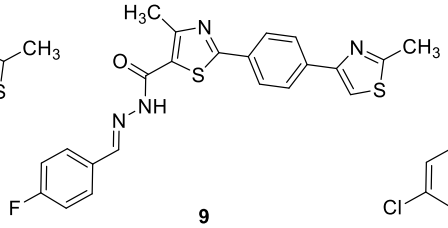


7

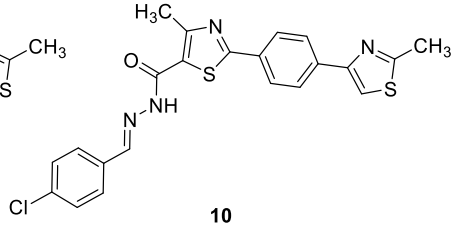
Anca-maria Borcea *et al*. [9] synthesized a series of compounds containing acylhydrazones bearing a 1,4-phenylene-bisthiazole scaffold, and evaluated their anti-candida activity. Compounds 8 and 9 have the best inhibitory activity on *Candida albicans* and *Candida parapsilosis*, while compound 10 has the highest inhibitory activity on *Candida parapsilosis*. The most sensitive fungal strain to newly synthesized compounds was *Candida krusei.*



8

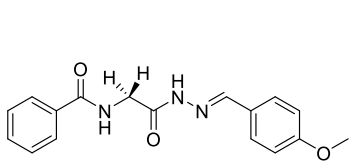


9

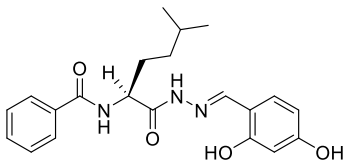


10

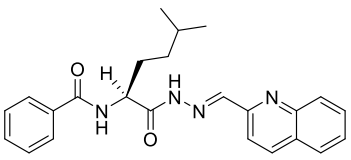
Obaid-ur-rahman Abid *et al*. [10] studied the synthesis of derivatives of acylhydrazone with antibacterial activity and cytotoxicity from *N*-benzoylated amino acids and different substituted aldehydes (11-15), which had broad-spectrum antibacterial activity and could be used as a major candidate compound for further biological research and structural modification.



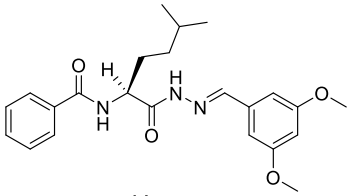
11



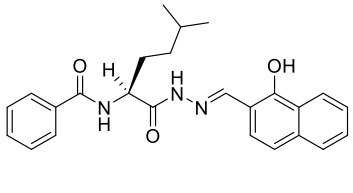
12



13



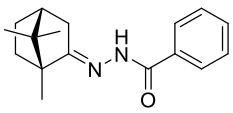
14



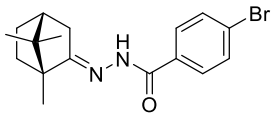
15

2.2 Antiviral activity

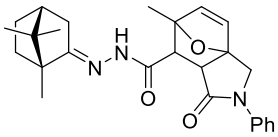
A virus is a small, simple organism that contains only one nucleic acid (DNA or RNA) and can only replicate in living cells of an organism. It infects all types of organisms, including humans, animals and plants. Some viruses are very dangerous to humans. A series of novel D-(+)-camphor *N*-acylhydrazones were synthesized and their antiviral activity was studied in vitro against vaccinia and influenza viruses. Compounds 16-18 showed low toxicity and the highest activity against vaccinia virus, compound 18 exhibited moderate activity against influenza virus [11].



16

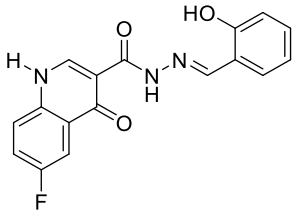


17

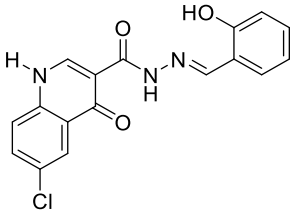


18

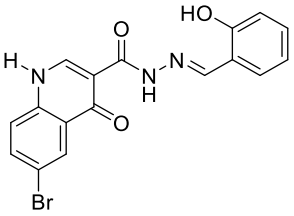
Roberta K. F. Marra *et al*. synthesized quinolone-*N*-acylhydrazone hybrids 19-21, which have shown good anti-arbovirus activity towards ZIKV and Chikungunya viruses, and non-toxic effect on Vero cells [12].



19

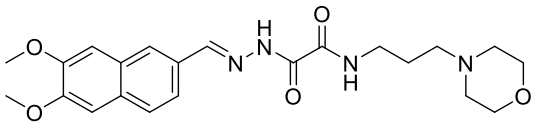


20

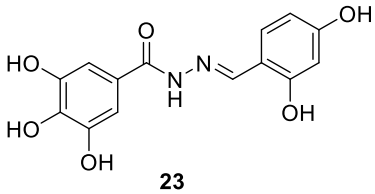


21

Acetic acid, 2-[[3-(4-morpholinyl) propyl] amino]-2-oxo-,2-[(3,4-dimethoxyphenyl) methylene] hydrazide (22) represents a novel neuraminidase inhibitor with IC_{50} value of 2.37 ± 0.5 *mM*[13]. (E)-*N'*-(2,4-dihydroxybenzylidene)-3,4,5-trihydroxybenzohydrazide (23) is considered as Dual target inhibitor of HIV-1 Integrase and Reverse Transcriptase Ribonuclease H and it is also able to inhibit viral replication in cell-based antiviral assays [14].



22

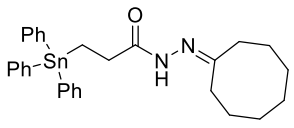


23

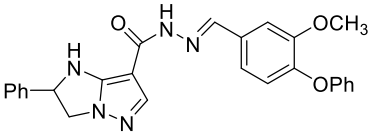
2.3 Antitumor activity

In medicine, cancer is a malignant tumor that originates in epithelial tissue and is the most common type of malignant tumor. Obaid-ur-rahman Abid *et al*. [10] characterized and evaluated the cytotoxicity of acylhydrazone synthesized from three amino acids, and the results showed that compounds 11, 13 and 14 had cytotoxicity and were expected to be candidates for anti-tumor or anticancer activity.

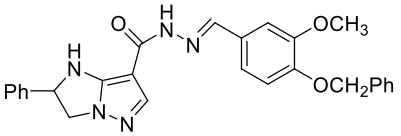
Xicheng Liu *et al*. [15] synthesized triphenyltin acylhydrazone Compound 24, which had higher cytotoxicity and certain selectivity for A549 lung cancer cells with IC_{50}=9.2*μM*. Chiara Brullo *et al*. [16] synthesized compounds 25 and 26 and showed good inhibitory effects on non-small Cell Lung cancer, colon cancer, ovarian cancer, kidney cancer, prostate cancer and melanoma.



24

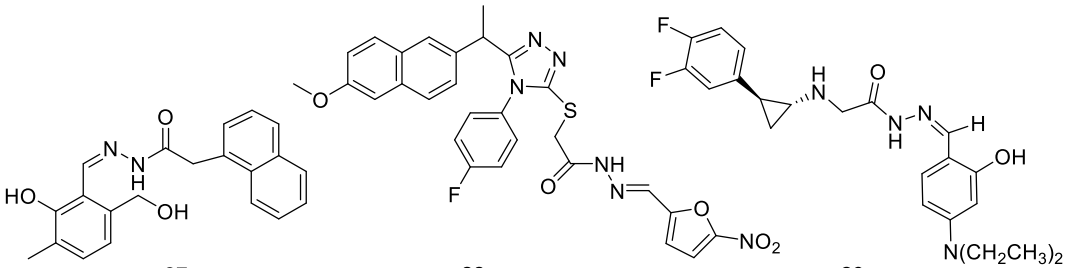


25



26

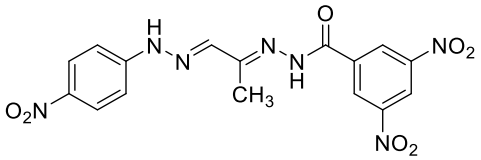
Xuyang Chen *et al*. [17] synthesized compound 27 with anti-tumor activity, which inhibited cell cycle and induced cell apoptosis by reducing intracellular Labile Iron Pool (LIP) and glutathione (GSH) content, and had anti-angiogenesis effect. Muhammed İ. Han *et al*. [18] synthesized a series of acylhydrazone derivatives, the study found that compound 28 for bladder tumor, renal cell carcinoma and prostate cancer has strong anticancer activity, IC_{50} value concentration were 26.0, 34.5, and 48.8*μM*. Kai Sun *et al*. [19] studied a series of Lysine specific demethylase 1(LSD1) inhibitors based on phenylalanine acylhydrazone, among which the most effective compound 29 can inactivate LSD1 with IC_{50}=91.83*nM*. At the cellular level, the accumulation of CD86 and H3K4me2 was induced, and the proliferation of gastric cancer cells was inhibited by inactivating LSD1.



27 28 29

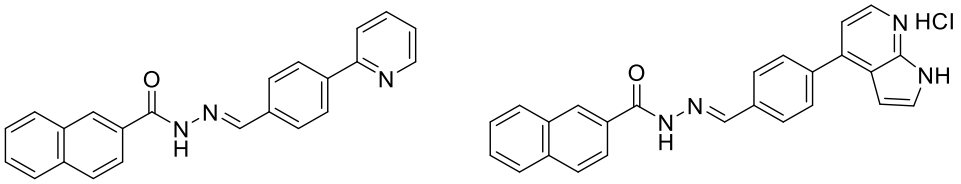
2.4 Anti-inflammatory and analgesic activity

Inflammation is a complex process produced by activated immune-related cells. Non-steroidal anti-inflammatory drugs are the essential drug of choice for treating inflammation and pain, but their severe side effects limit their use in common inflammation and painkillers, so it is necessary to look for anti-inflammatory drugs with fewer side effects. Cássio S. Meira *et al*. [20] synthesized and screened compound 30, which could inhibit lymphocyte proliferation and cytokine production by inhibiting IL-1b secretion and inhibiting the production of nitric oxide in activated macrophages, followed by the reduction of COX2 expression and PGE2 biosynsynthesis.



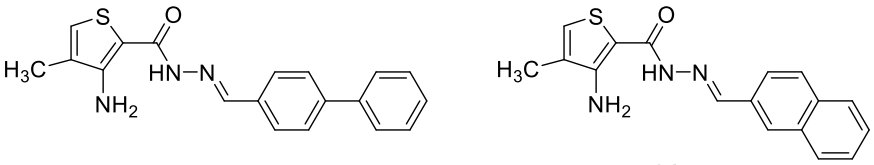
30

Rosana H.C.N. Freitas *et al*. [21] synthesized compound 31, which has anti-inflammatory activity by inhibiting or reducing the ability of cell migration. Isabella A. Guedes *et al*. [22] developed a new 7-azaindol *N*-acylhydrazone (32) and able to inhibit IκB kinase 2 (IKK2) with an IC_{50} value of 3.8μM.



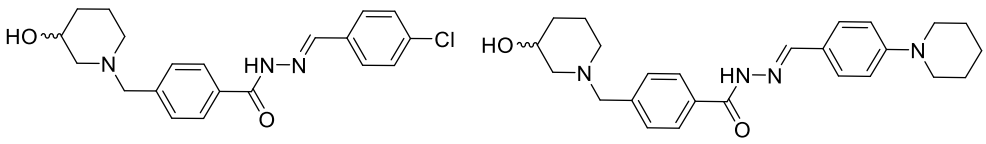
31 32

Herrmann S. *et al*. [23] synthesized compounds 33 and 34 that have antinociceptive activity and are regarded as promising analgesic lead-candidates for further investigation.



33 34

Náthalia M. dos Santos *et al*. [24] synthesized compounds 35 and 36 that can reduce neuropathic pain induced by chronic constriction injury and thermal threshold in tail swinging test.



35 36

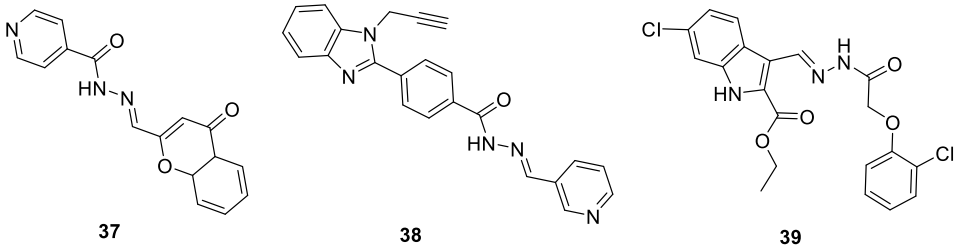
2.5 Central nervous system activity

Central nervous system symptoms were disease storage within the brain tissue after the cholinesterase inhibition, make the central excited passed obstacles between nerve cells, causing the central nervous system disorders. Daniela Correa Santos *et al*. [25] synthesized acylhydrazone derivatives from

isoniazone, and found that compound 37 was the only compound with significant inhibitory effect on acetylcholinesterase (54%, 100 μM), chlorination mechanism related Myeloperoxidase(MPO) inhibition (IC_{50} = 5.3±0.5 μM), antioxidant capacity (IC_{50} = 42.4±1.9 μM), and good chelating properties of biological metals (Fe2+ and Zn2+).

Özgür Devrim Can *et al*. [26] synthesized non-cytotoxic and non-genotoxic compound 38 with human Monoamine oxidase B inhibition, which is useful for the treatment of Parkinson's disease and Alzheimer's disease.

Flávia Pereira Dias Viegas *et al*. [27] synthesized an against neurodegenerative disease compound 35, showing the best in *silico* ADME parameters, AChE selective inhibition, anti-inflammatory and neuroprotective properties in vivo and in vitro models.

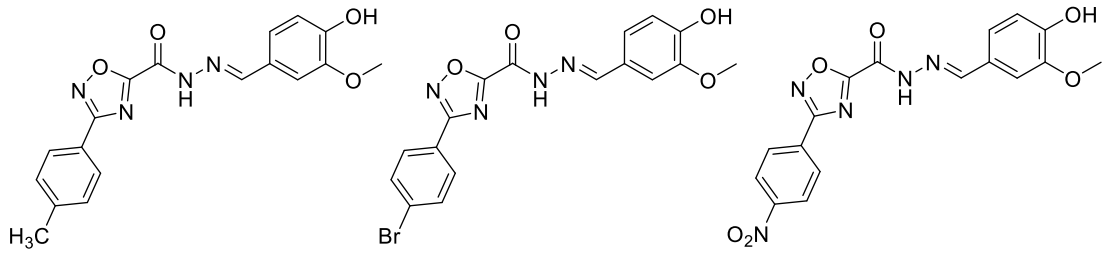


37 38 39

Ramon van der Vlag *et al*. [28] synthesized a compound 39 that inhibits 15-lipoxysinase-1 with an IC_{50} value of 0.23±0.0μM and has potential for treatment of asthma, diabetes, stroke, Alzheimer's disease, Parkinson's disease and cancer.

2.6 Antiprotozoal activity

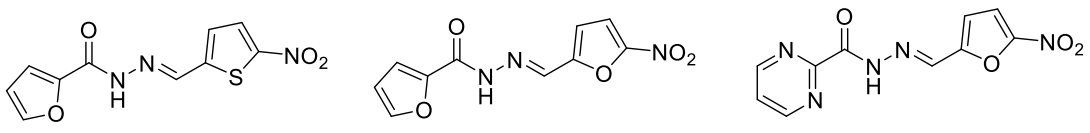
Malaria is a parasitic disease caused by human plasmodium infection. It is a global epidemic disease, mainly concentrated in tropical and subtropical areas. José Maurício DOS Santos Filho *et al*.[29] synthesized compounds 40, 41 and 42 that were effective and selective against malarial activity of P. berghei.



40 41 42

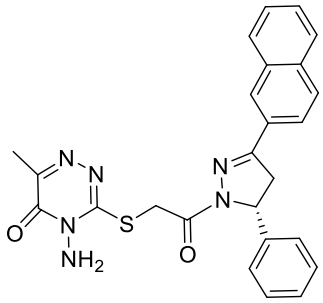
Furanyl *N*-acylhydrazone Derivatives with anti-vaginal trichomonad activity were synthesized by Mirna Samara Dié Alves *et al*. [30]. Compounds 43 and 44 were at 6.25μM, with IC_{50} of 1.69μM and 1.98μM, respectively, which induced complete parasite death 24 hours after exposure.

Elaine Soares Coimbra *et al*.[31] synthesize compound 45 with antileishmanial activity, IC_{50}=10.8μM.

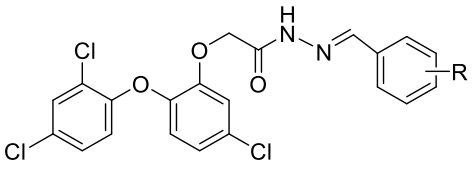


43 44 45

The derivatives of *N*-acylhydrazone were synthesized by V Eronica Herera-Mayorga *et al*. [32] and evaluated for their trypanosomicidal activity and enzyme inhibition in vitro. Compound 46 showed the best trypanocidal activity against epimatigote (IC_{50}= 36.26 ± 9.9 μM) and trypomastigote (IC_{50}= 166.21± 14.5 μM and 185.1 ± 8.5 μM on NINOA and INC-5 strains, respectively) forms of *Trypanosoma cruzi*. Sebastian Vergara *et al*. [33] synthesized 11 triclosan–hydrazone compounds (47) and performed in vitro evaluation of the intracellular anflagellate body of *Leishmania* and *Trypanosomes*, indicating that these compounds may be potential templates for the development of antigenic against protozoal diseases drugs.



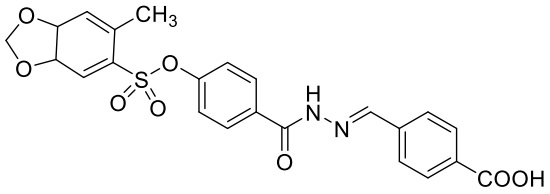
46



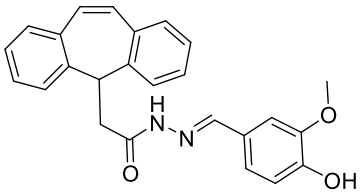
47

2.7 Other biological activities

Avia s. Frattani *et al*. [34] synthesized compound **48** in treatment of thromboembolic disease. *N*-acylhydrazone with dibenzo[a,d][7]annulene moiety (**49**) exhibited the highest antioxidant activity using the DPPH method[35].



48



49

3. Conclusions

This review concisely summarizes the biological activities of *N*-Acylhydrazones reported in recent five years. *N*-Acylhydrazones not only exhibited antimicrobial, antiviral, antitumor, anti-inflammatory, analgesic, anti-central system disorder and antiprotozoal biological activities, but also showed antithrombotic and antioxidant biological activities. Owing to their ease of synthesis and diverse biological activities, it has great potential in future drug research and development.

References

[1] S. Thota, D.A. Rodrigues, P.D. Pinheiro, et al. N-Acylhydrazones as drugs. Bioorganic & Medicinal Chemistry Letters, Vol. 28 (2018) No. 17, p. 2797-2806.

[2] R.D. Maia, R. Tesch, C.A. Fraga, et al. Acylhydrazone derivatives: a patent review. Expert Opinion on Therapeutic Patents, Vol. 24 (2014) No. 11, p. 1161-1170.

[3] Z. Zhou, T.T. Zhou, Synthesis and antibacterial activity of c-7 acylhydrazone derivatives of dehydroabietic acid. Journal of Chemical Research, Vol. 42 (2018) No. 8, p. 405-407.

[4] J. Yang, X.R. Liu, M.K. Yu, W. B. Yang, Z.W. Yang, S.S. Zhao. Co and cu complexes with 2-acetylpyridine-4-hydroxy phenylacetyl acylhydrazone: synthesis, crystal structures, ct-dna/bsa binding behaviors, antibacterial activities and molecular docking studies. Polyhedron,Vol. 187 (2020) , p. 114619.

[5] A.V. Bogdanov, I.F. Zaripova, A.D. Voloshina, A.S. Sapunova, N.V. Kulik, & J.K. Voronina, et al. Synthesis and antimicrobial study of novel 1-benzylated water-soluble isatin-3-hydrazones. Chemistry & Biodiversity. Vol. 15 (2018) No. 6, p. e1800088.

[6] M. Aarjane, A. Aouidate, S. Slassi, & A. Amine. Synthesis, antibacterial evaluation, in silico admet and molecular docking studies of new n-acylhydrazone derivatives from acridone. Arabian Journal of Chemistry. Vol. 13 (2020) No. 7, p. 6236-6245.

[7] Ł. Popiolek, A. Biernasiuk, A. Berecka, A. Gumieniczek, A. Malm, & M. Wujec. New hydrazide–hydrazones of isonicotinic acid: synthesis, lipophilicity and in vitro antimicrobial screening. Chemical Biology & Drug Design,Vol. 91 (2018) No. 4, p. 915-923.

[8] Ł. Popiolek, B. Rysz, A. Biernasiuk, & M. Wujec. Synthesis of promising antimicrobial agents: hydrazide-hydrazones of 5-nitrofuran-2-carboxylic acid. Chemical Biology & Drug Design, Vol. 95 (2020) No. 2, p.260-269.

[9] A. Borcea, G. Marc, I. Ionuț, D.C. Vodnar, L. Vlase, F. Gligor, & O. Oniga. A Novel Series of Acylhydrazones as Potential Anti-Candida Agents: Design, Synthesis, Biological Evaluation and In Silico Studies. Molecules (Basel, Switzerland), Vol. 24 (2019) No. 1, p. 184.

[10] O. Abid, G. Khatoon, M. Arfan, I. Sajid, P. Langer, W. Rehman, & K.S. Haleem. Synthesis of Hydrazones from Amino Acids and their Antimicrobial and Cytotoxic Activities. Journal of The Chinese Chemical Society, Vol. 64(2017) No. 9, p. 1079-1087.

[11] K.S. Kovaleva, F.I Zubkov, N.I. Bormotov, et al. Synthesis of D-(+)-camphor-based N-acylhydrazones and their antiviral activity. MedChemComm, Vol. 9(2018) No. 12, p. 2072–2082.

[12] R.K. Marra, A.E. Kummerle, G.P. Guedes, et al.Quinolone-N-acylhydrazone hybrids as potent Zika and Chikungunya virus inhibitors. Bioorganic & Medicinal Chemistry Letters, Vol. 30 (2020) No. 2, p. 126881.

[13] Z.X. Zhao, L.P. Cheng, M. Li, W. Pang, & F.H. Wu. Discovery of novel acylhydrazone neuraminidase inhibitors. European Journal of Medicinal Chemistry. Vol. 173(2019), p. 305-313.

[14] M. Carcelli, D. Rogolino, A. Gatti, et al. Chelation Motifs Affecting Metal-dependent Viral Enzymes:N'-acylhydrazone Ligands as Dual Target Inhibitors of HIV-1 Integrase and Reverse Transcriptase Ribonuclease H Domain. Frontiers in Microbiology, Vol. 8(2017), p. 440.

[15] X. Liu, Y. Tang, X. He, et al. Triphenyltin(IV) acylhydrazone compounds: Synthesis, structure and bioactivity. Journal of Inorganic Biochemistry, Vol. 191 (2019), p. 194-202.

[16] C. Brullo, F. Rapetti, S. Alfei, et al. Discovery of new antiproliferative imidazopyrazole acylhydrazones able to interact with microtubule systems. ChemMedChem, Vol. 15 (2020) No. 11, p. 961-969.

[17] X. Chen, H. Li, H. Luo, Z. Lin, & W. Luo. Synthesis and evaluation of pyridoxal hydrazone and acylhydrazone compounds as potential angiogenesis inhibitors. Pharmacology, Vol. 104 (2019) No. 5-6, p. 244-257.

[18] M. Han, H. Beki, A.I. Uba, Y. Yldrm, et al. Synthesis, molecular modeling, in vivo study, and anticancer activity of 1,2,4-triazole containing hydrazide–hydrazones derived from (s)-naproxen. Archiv der Pharmazie, Vol. 352 (2019) No. 21, p. e1800365.

[19] K. Sun, J. Peng, F. Suo, T. Zhang, et al. Discovery of tranylcypromine analogs with an acylhydrazone substituent as LSD1 inactivators: Design, synthesis and their biological evaluation. Bioorganic & Medicinal Chemistry Letters, Vol. 27 (2017) No. 22, p. 5036-5039.

[20] C.S. Meira, J.M. Filho, C.C. Sousa, et al. Structural design, synthesis and substituent effect of hydrazone-N-acylhydrazones reveal potent immunomodulatory agents. Bioorganic & Medicinal Chemistry, Vol. 26 (2018) No. 8, p. 1971-1985.

[21] R.H. Freitas, N.M. Cordeiro, P.R. Carvalho, et al. Discovery of naphthyl-N-acylhydrazone p38α MAPK inhibitors with in vivo anti-inflammatory and anti-TNF-α activity. Chemical Biology & Drug Design, Vol. 91 (2018) No. 2, p. 391-397.

[22] I.A. Guedes, R.H. Freitas, N.M. Cordeiro, et al. Lassbio-1829 hydrochloride: development of a new orally active n-acylhydrazone ikk2 inhibitor with anti-inflammatory properties. Chemmedchem, Vol. 11 (2016) No. 2, p. 234-244.

[23] S. Herrmann, T. Schubel, F.N. Costa, et al. Synthesis, X-ray diffraction study and pharmacological evaluation of 3-amino-4-methylthiophene-2-acylcarbohydrazones. Anais Da Academia Brasileira De Ciencias, Vol. 90 (2018) No. 1, p. 1073-1088.

[24] N.M. Santos, N.C. Pereira, A.P. De Albuquerque, et al. 3-hydroxy-piperidinyl-n-benzyl-acyl-arylhydrazone derivatives reduce neuropathic pain and increase thermal threshold mediated by opioid system. Biomedicine & Pharmacotherapy, Vol. 99(2018), p. 492-498.

[25] Daniela Corrêa Santos a, B, R. R. H., Marcos Antonio de Abreu Lopes Junior a c, et al. Acylhydrazones as isoniazid derivatives with multi-target profiles for the treatment of alzheimer's disease: radical scavenging, myeloperoxidase/acetylcholinesterase inhibition and biometal chelation. Bioorganic & Medicinal Chemistry, Vol. 28 (2020) No. 10), p. 115470.

[26] O.D. Can, D. Osmaniye, U.D. Ozkay, et al. MAO enzymes inhibitory activity of new benzimidazole derivatives including hydrazone and propargyl side chains. European Journal of Medicinal Chemistry, Vol. 131 (2017), p. 92-106.

[27] F.P. Viegas, M.D. Silva, M.D. Rocha, et al. Design, synthesis and pharmacological evaluation of N-benzyl-piperidinyl-aryl-acylhydrazone derivatives as donepezil hybrids: Discovery of novel multi-target anti-alzheimer prototype drug candidates. European Journal of Medicinal Chemistry, Vol. 147 (2018), p. 48-65.

[28] R.V. Der Vlag, H. Guo, U. Hapko, et al. A combinatorial approach for the discovery of drug-like inhibitors of 15-lipoxygenase-1. European Journal of Medicinal Chemistry, Vol.174(2019), p.45-55.

[29] J.M. Filho, D. Silva, T.S. Macedo, et al. Conjugation of n-acylhydrazone and 1,2,4-oxadiazole leads to the identification of active antimalarial agents. Bioorg Med Chem, Vol. 24 (2016) No. 22, p. 5693-5701.

[30] A. Msd, D.N. Rn, Â. Senalopes, et al. Antiparasitic activity of furanyl n-acylhydrazone derivatives against trichomonas vaginalis: in vitro and in silico analyses. Parasites & Vectors, Vol. 13 (2020) No. 1, p. 59.

[31] E.S. Coimbra, Marcus Vinícius Nora de Souza, M.S. Terror, et al. Synthesis, biological activity, and mechanism of action of new 2-pyrimidinyl hydrazone and n-acylhydrazone derivatives, a potent and new classes of antileishmanial agents. European Journal of Medicinal Chemistry, Vol. 184 (2019), p. 111742.

[32] V. Herreramayorga, E.E. Lararamirez, K.F. Chaconvargas, et al. Structure-Based Virtual Screening and In Vitro Evaluation of New Trypanosoma cruzi Cruzain Inhibitors. International Journal of Molecular Sciences, Vol. 20 (2019) No. 7, p. 1742.

[33] S. Vergara, M. Carda, R. Agut, et al. Synthesis, antiprotozoal activity and cytotoxicity in U-937 macrophages of triclosan–hydrazone hybrids. Medicinal Chemistry Research, Vol. 26 (2017) No. 12, p. 3262-3273.

[34] F.S. Frattani, L.M. Lima, E.J. Barreiro, et al. The antithrombotic and haemostatic effects of LASSBio-752: a synthetic, orally active compound in an arterial and venous thrombosis model in rats. Journal of Pharmacy and Pharmacology, Vol. 69 (2017) No. 10, p. 1374-1380.

[35] L.I. Socea, D.C. Visan, S.F. Barbuceanu, et al. The Antioxidant Activity of Some Acylhydrazones with Dibenzo[a,d][7]annulene Moiety. Revista de chimie, Vol. 69 (2018) No. 4, p. 795-797.