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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME PHENYL ACETIC ACID HYDRAZONE DERIVATIVES

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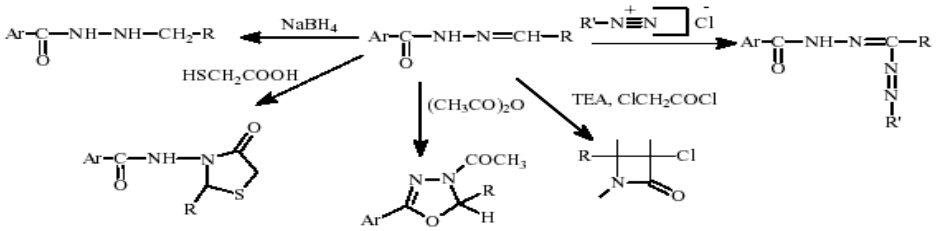
ABSTRACT
These products are the result of further operation after the derivation of three hydrazones derivative compounds-
N'-(4-Chlorobenzylidene)-2-phenylacetohydrazide
N'-(2chlorobenzylidene)-2-phenylacetohydrazide
N'-(3, 4, 5-trimethoxybenzylidene)-2-phenylacetohydrazide
N'-(furan-2-ylmethylene)-2-phenylacetohydrazide
N'-(3, 4, 5-Trimethoxybenzylidene)-2-phenylacetohydrazide
N'-(1-(4-hydroxyhenyl) ethylidene)-2-phenylacetohydrazide
These make a considerable interest in process development of novel compounds with anticonvulsant, antidepressant, analgesic, and anti-inflammatory, anti platelet, anti malarial, antimicrobial, antimycobacterial, antitumoral, vasodilator, and antiviral and antis chistosomiasis activities. These all three compounds evaluated their biological activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.
Keywords: Hydrazones, Hydrazide-Hydrazones, Phenyl Acetic Acid, Anti-inflammatory Activity, Biological Activity.

INTRODUCTION

Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, and analgesic, anti-inflammatory, and ant platelet, ant tubercular and antitumoral activities. For example, isonicotinoyl hydrazones are antitubercular; 4-hydroxybenzoic acid[(5-nitro-2-furyl)ethylene]-hydrazide (nifuroxazide) is an intestinal antiseptic; 4-fluorobenzoic acid[(5-nitro-2-furyl)methylene]-hydrazide[1] and 2,3,4-pentanetrione-3-[4-[[(5-nitro-2-furyl)methylene]hydrazino]carbonyl]phenyl]-hydrazone[2], which were synthesized in our Department, have antibacterial activity against both*Staphylococcus aureus* ATCC 29213 and *Mycobacterium tuberculosis* H37Rv at a concentration of 3.13 µg/mL.*N*1-(4-Methoxybenzamido)benzoyl]-*N*2-[(5-nitro-2-furyl)methylene]hydrazine, which was also synthesized in our Department[3], demonstrated antibacterial activity. In addition, some of thenew hydrazide-hydrazones that we have recently synthesized were active against the same strain of *M. tuberculosis* H37Rv between the concentrations of 0.78-6.25 µg/mL[4].

General procedure

Hydrazide-hydrazones compounds are not only intermediates but they are also very effective organic compounds in their own right. When they are used as intermediates, coupling products can be synthesized by using the active hydrogen component of –CONHN=CH- azometine group[8]. *N*-Alkyl hydrazides can be synthesized by reduction of hydrazones with $NaBH_4$[9], substituted 1,3,4- oxadiazolines can be synthesized when hydrazones are heated in the presence of acetic anhydride [1,10,11]. 2-Azetidinones can be synthesized when hydrazones react with trietylamine chloro acetylchloride[12]. 4-Thiazolidinones are synthesized when hydrazones react with thioglycolic acid/ thiolactic acid[3,13].



Scheme -1

OUTLINE ABOUT PREVIOUS COMPOUNDS

Comp.Code	Name	Mol. Formula	Mol. Wt	M.P. (°C)
GL[1]	N'-(4-Chlorobenzylidene)-2-phenylacetohydrazide	$C_{15}H_{13}N_2OCl$	272	61
GL[2]	N'-(2-Chlorobenzylidene)-2-phenylacetohydrazide	$C_{15}H_{13}N_2OCl$	272	60.5
GL[3]	2-Phenyl-N'-(1-(2,3,4-trimethoxyphenyl)ethylidene)acetohydrazide	$C_{13}H_{12}N_2O_2$	228	55.5
GL[4]	N'-(furan-2-ylmethylene)-2-phenylacetohydrazide	$C_{18}H_{20}N_2O_4$	328	50.5
GL[5]	N'-(3,4,5-Trimethoxybenzylidene)-2-phenylacetohydrazide	$C_{17}H_{17}N_2O_2$	281	71
GL[6]	N'-(1-(4-hydroxyhenyl)ethylidene)-2-phenylacetohydrazide	$C_{16}H_{16}N_2O_2$	268	51

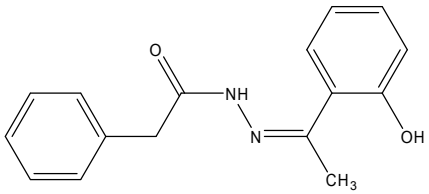
MATERIALS AND METHODS

All the melting points reported in this dissertation progress report were determined by open capillary tube method and are uncorrected. The synthetic and analytical studies of the compounds were carried out using laboratory grade and analytical grade reagents as the case may be standard procedure or reported methods were followed with or with out modification appropriately as and when required.

General methodology for experimental compound

Synthesis of N'-(1-(2-hydroxyphenyl)ethylidene)-2-phenylacetohydrazide: (GL^7)

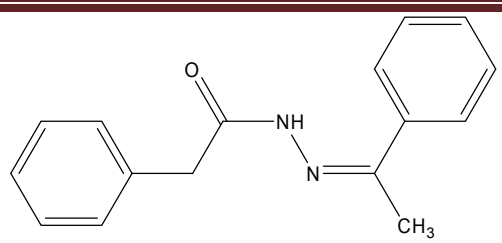
A mixture of o-hydroxy acetophenone (1.36gm, 0.01mole) and 2-phenyl acetohydrazide (1.5gm, 0.01mole) were dissolved in methanol then two drops of conc. HCl were added as catalyst and stirred at room temperature for 5 hr. the reaction mixture was poured into ice and filtered. The crude product so obtained was dried and recrystallized with methanol.



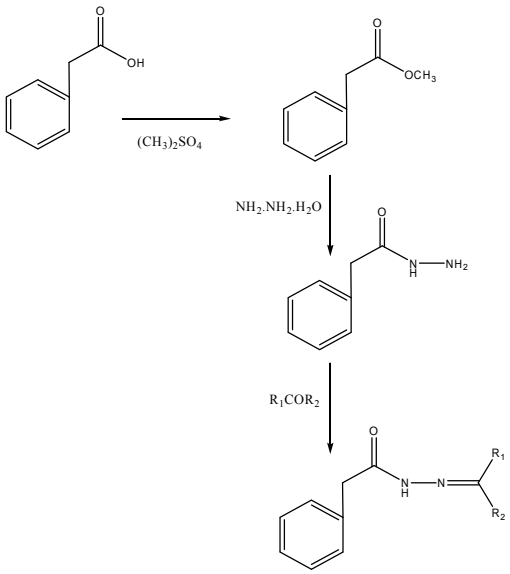
N'-(1-(2-hydroxyphenyl)ethylidene)-2-phenylacetohydrazide

Synthesis of N'-(1-phenyl ethylidene)-2-phenylacetohydrazide: (GL^8)

A mixture of acetophenone (1.28gm, 0.01mole) and 2-phenyl acetohydrazide (1.5gm, 0.01mole) were dissolved in methanol then two drops of conc. HCl were added as catalyst and stirred at room temperature for 4 hr. the reaction mixture was poured into ice and filtered. The crude product so obtained was dried and recrystallized with methanol.



N'-(1-phenyl ethylidene)-2-phenylacetohydrazide



General methodology Scheme-2

Table – 1: The Physico-chemical data of synthesized compounds

Comp.Code	Mol. Formula	Mol. Wt .	F_{ro}	Color (Appearance)	M.P. (°C)	λ_{max}
GL^7	$C_{16}H_{16}N_2O_2$	268	0.85[b]	Black	53	258.329
GL^8	$C_{16}H_{16}N_2O$	252	0.90[c]	Light brown	61.5	330.805

Solvent System:
a. (Chloroform: Methanol 8:2), b. (Chloroform :Methanol 8 : 1)

Table -2: IR Data of the title compounds

Compound	IR (cm^{-1})
GL^7	3396.67(OH), 3157.1(NH), 2951.76(Ar-CH), 2896(CH_3)$_3$, 1685.3(C=O), 1630.54(C=N)

BIOLOGICAL ACTIVITY OF HYDRAZONE COMPOUNDS

Anticonvulsant Activity

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archived during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of Epilepsy to characterize the anticonvulsant activity. The biological results revealed that in general, the acetylhydrazones **2** provided good protection against convulsions while the oxamoylhydrazones **3** were significantly less active. [21].

Analgesic, Anti-inflammatory and Anti platelet Activity

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the hydrazone moiety present in some compounds possess a pharmacophoric character for the inhibition of COX. The most important anti-inflammatory derivative 2-(2-formylfuryl) pyridylhydrazone **7** presented a 79 % inhibition of pleurisy at a dose of 80.1 mol/kg. The authors also described the results concerning the mechanism of the action of these series of *N*-heterocyclic derivatives in platelet aggregation that suggests a Ca2+ scavenger mechanism. Compound **7** was able to complex Ca2+ in invitro experiments at 100 concentrations, indicating that these series of compounds can act as Ca2+ scavenger depending on the nature of the aryl moiety present at the imine subunit [22].

Antimycobacterial Activity

Tuberculosis is a serious health problem that causes the death of some three million people every year worldwide [23]. In addition to this, the increase in *M. tuberculosis* strains resistant to front-line antimycobacterial drugs such as rifampin and INH has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of tuberculosis. Meyer

and Mally prepared new hydrazones by reacting isoniazid (INH) with benzaldehyde, o-chlorobenzaldehyde
And vanillin [5]. Shchukina *et al*. prepared INH hydrazide-hydrazones **1** by reacting INH with various aldehydes and ketones; the compounds were reported to have activity in mice which had been infected with various strains of *M. tuberculosis*, and also indicated lower toxicity than INH [5,6].
The reaction of 1-methyl-1H-2-imidazo [4, 5-b] pyridine carboxylic acid hydrazide with substituted aldehydes yielded the corresponding hydrazide-hydrazones. Compound **32** exhibited antimycobacterial activity against *M.tuberculosis H37 Rv, M. tuberculosis 192, M. tuberculosis 210*, isolated from patients and resistant against INH, ethambutol, rifampicine at 31.2 ìg/mL [24].

Antitumoral Activity

A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several hydrazones having antitumoral activity. Some of diphenolic hydrazones showed maximum uterotrophic inhibition of 70%, whereas compound **58** exhibited cytotoxicity in the range of 50-70% against MCF-7 and ZR-75-1 human malignant breast cell lines [25].

Antimicrobial Activity

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists. Ethyl 2-arylhydrazono-3-oxobutyrates 17 were synthesized in order to determine their antimicrobial properties. Compound 17d showed significant activity against *S. aureus* whereas the others had no remarkable activity on this strain. Compound 17e was found to be more active than the others against *Mycobacterium fortuitum* at a MIC value of 32 ìg/ml [26].

RESULT & DISCUSSION

The synthesized compounds were purified and the purity of all compounds was checked by melting point and RF value determination. The structures of this compound were established by recording spectral data (Table-1, 2 & 3). In the present work synthesized hydrazones derivative compound significantly expected to show Anticonvulsant Activity, Analgesic, Anti-inflammatory Antiplatelet Activity Antimycobacterial Activity, and Antimicrobial Activity.

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