FACILE INTRAMOLECULAR CYCLIZATION OF *N*-(2-HYDROXYBENZOYL)HYDRAZONES TO *N*,*N*'-DIACETYL BENZO-1,3,4-OXADIAZEPINE DERIVATIVES

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FACULTY OF SCIENCE
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DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
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2018

UNIVERSITY OF MALAYA

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FACILE INTRAMOLECULAR CYCLIZATION OF *N*-(2-HYDROXYBENZOYL)HYDRAZONES TO *N*,*N*'-DIACETYL BENZO-1,3,4-OXADIAZEPINE DERIVATIVES

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FACILE INTRAMOLECULAR CYCLIZATION OF *N*-(2-HYDROXYBENZOYL)HYDRAZONES TO *N*,*N*'-DIACETYL BENZO-1,3,4-OXADIAZEPINE DERIVATIVES

ABSTRACT

The synthesis of seven-membered benzo-1,3,4-oxadiazepines can be carried out through one-step intramolecular cyclization of *N*-(2-hydroxybenzoyl)hydrazones. The reaction was catalyzed by 4.50% (*v/v*) of sulfuric acid in acetic anhydride (V_t = 1 mL) at room temperature. The catalytic and substituent effects on the reactivity of this intramolecular cyclization were investigated. Through this strategy, a series of benzo-1,3,4-oxadiazepine derivatives were prepared (with yield up to 83%). These new heterocyclic compounds were characterized through their melting point, NMR and HRMS (ESI). It was observed that when electron-withdrawing group is at the *para* position of salicylic ring and electron-donating group at the *para* position of benzylidene ring, a good yield of seven-membered benzoxadiazepines were obtained. This strategy provided good method to a variety of substitution.

Keywords: benzo-1,3,4-oxadiazepine, Brønsted acids, cyclization, hydrazones, substituent effects.

KAEDAH PENGELANGAN INTRAMOLEKUL *N*-(2-HIDROKSIBENZOIL)HIDRAZON MUDAH UNTUK PEMBENTUKAN SEBATIAN *N*,*N*'-DIASETIL BENZO-1,3,4-OXADIAZEPIN

ABSTRAK

Sintesis gelang tujuh benzo-1,3,4-oxadiazepin boleh dilakukan melalui satu langkah pengelangan intramolekul *N*-(2-hidroksibenzoil)hidrazon. Tindak balas ini dimangkin oleh 4.50% (*v/v*) asid sulfuric dalam anhidrida asetik (V_t = 1 mL) pada suhu bilik. Kesan-kesan pemangkinan dan kumpulan penukar ganti terhadap kereaktifan pengelangan intramolekul telah dikaji. Melalui strategi ini, satu siri benzo-1,3,4-oxadiazepin telah berjaya disediakan (dengan peratusan hasil sehingga 83%). Sebatian heterosiklik baru ini telah dicirikan melalui takat lebur, spektroskopi resonans magnet nukleus (RMN) dan spektrometri jisim leraian tinggi. Kajian menunjukkan apabila kumpulan penarik elektron berada pada kedudukan *para* pada gelang salisilik dan kumpulan penderma elektron juga pada kedudukan *para* pada gelang benzilidin, gelang tujuh benzoxadiazepin telah dihasilkan dengan baik. Strategi ini adalah cara yang terbaik bagi penghasilan *N*-(2-hidroksibenzoil)hidrazon yang mempunyai pelbagai kumpulan penukar ganti.

Kata kunci: benzo-1,3,4-oxadiazepin, asid Brønsted, pengelangan, hidrazon, kesan kumpulan penukar ganti.

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LIST OF SYMBOLS AND ABBREVIATIONS

^{13}C	:	Carbon-13
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
$CDCl_3$	:	Deuterated chloroform
Cl	:	Chlorine atom
CN	:	Cyano
COOMe	:	Methoxycarbonyl
$CSCl_2$	:	Thiophosgene
d	:	Doublet
dd	:	Doublet of doublets
DMF	:	Dimethylformamide
DMSO-d_6	:	Deuterated dimethyl sulfoxide
EDG	:	Electron-donating groups
Et_3N	:	Triethylamine
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
EWG	:	Electron-withdrawing groups
h	:	Hour
H	:	Hydrogen atom
H_2SO_4	:	Sulfuric acid
HBr	:	Hydrogen bromide
HCl	:	Hydrochloric acid
HRMS (ESI)	:	High-Resolution Mass Spectrometry (Electrospray Ionization)
J	:	Coupling constant in Hz

$KHSO_4$	:	Potassium hydrogen sulfate
m	:	Multiplet
m.p.	:	Melting point
m.w.	:	Molecular weight
Me	:	Methyl
MeOH	:	Methanol
MS	:	Molecular sieves
$N_2H_4.H_2O$	:	Hydrazine hydrate
Na_2CO_3	:	Sodium carbonate
$NaHCO_3$	:	Sodium bicarbonate
$NaSO_4$	:	Sodium sulfate
NMR	:	Nuclear Magnetic Resonance
NO_2	:	Nitro
OMe	:	Methoxy
Ph_3PBr_2	:	Triphenylphosphine dibromide
r.t.	:	Room temperature
s	:	Singlet
SMe	:	Thiomethyl
t	:	Triplet
td	:	Triplet of doublets
TFA	:	Trifluoracetic acid
TLC	:	Thin Layer Chromatography
TMS	:	Tetramethylsilane
UV	:	Ultraviolet
V_t	:	Total volume
δ	:	Chemical shift in ppm

CHAPTER 1: INTRODUCTION

1.1 Benzoxadiazepines

Heterocycles containing more than one heteroatom appear to be attractive targets in organic chemistry due to their chemical reactivities as well as their potential biological properties. Convenient method for the synthesis of such species, that is, benzoxadiazepines remains a challenge.

Benzoxadiazepines are fused heterocycles resulting from the combination of benzene ring and oxadiazepine — a seven-membered heterocycle bearing one oxygen and two nitrogen atoms. There is a total of nine isomeric oxadiazepine parent compounds, together with the numbering of their atoms, are displayed in Figure 1.1.

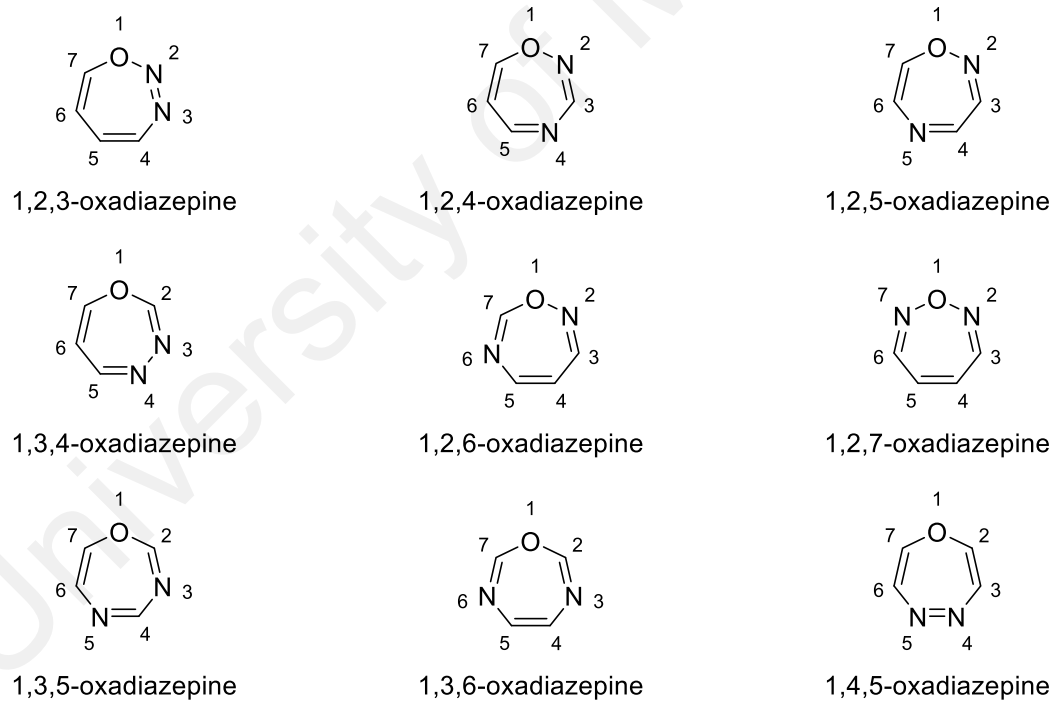


Figure 1.1. Nine isomeric oxadiazepine parent compounds.

Theoretically, sixteen benzoxadiazepine isomers can be derived from these nine oxadiazepine isomers. Ten isomers of benzoxadiazepine (Figure 1.2) are already reported in the literature whilst the remaining six benzoxadiazepine isomers (Figure 1.3) remain unreported.

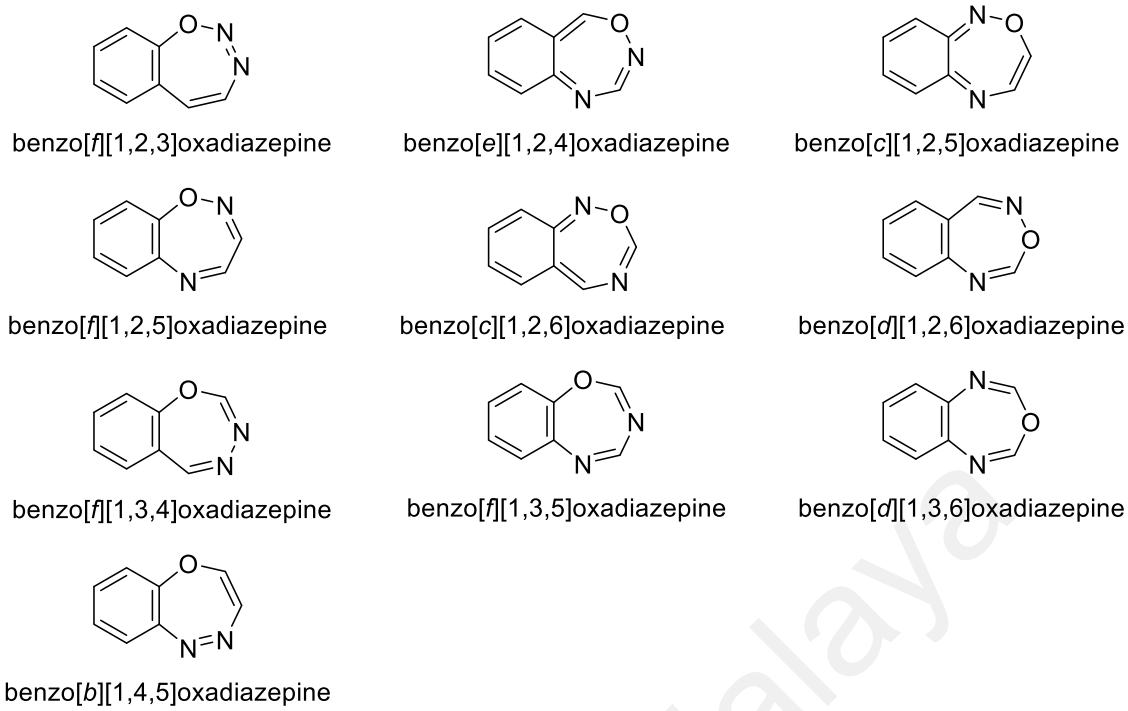


Figure 1.2. Skeletons of ten known benzoxadiazepine isomers.

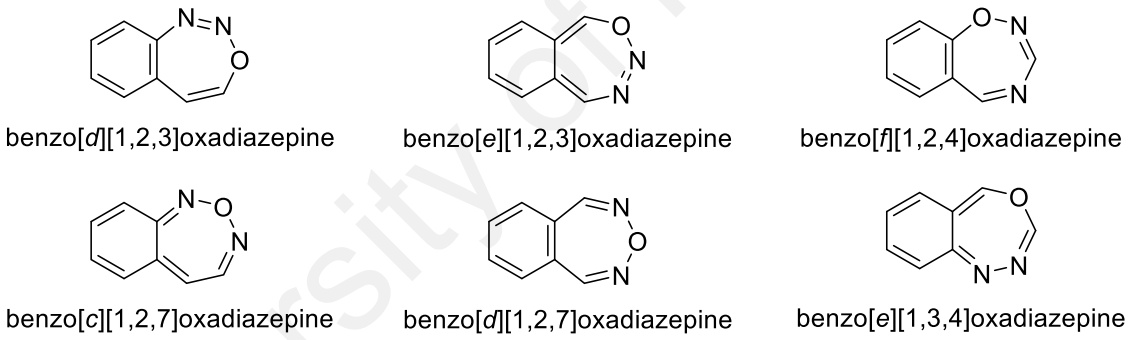


Figure 1.3. Skeletons of six unknown benzoxadiazepine isomers.

1.2 Importance of Oxadiazepines and Benzoxadiazepines in Medicinal Chemistry and Organic Syntheses

Oxadiazepines have been found to exhibit diverse pharmacological effects. For example, compound **1** has been shown to possess appreciable activity against gamma secretase modulator for the treatment of Alzheimer's disease (Li *et al.*, 2013). Moreover, compounds **2** and **3** show antimicrobial properties (El-Badry & Taha, 2011; Khalil & Habib, 1990), compound **4** as anticancer (D'Errico *et al.*, 2012), compound **5** as herbicides (Muehlebach *et al.*, 2009) and compound **6** as cytotoxicity activities (Abele *et al.*, 2012) (Figure 1.4).

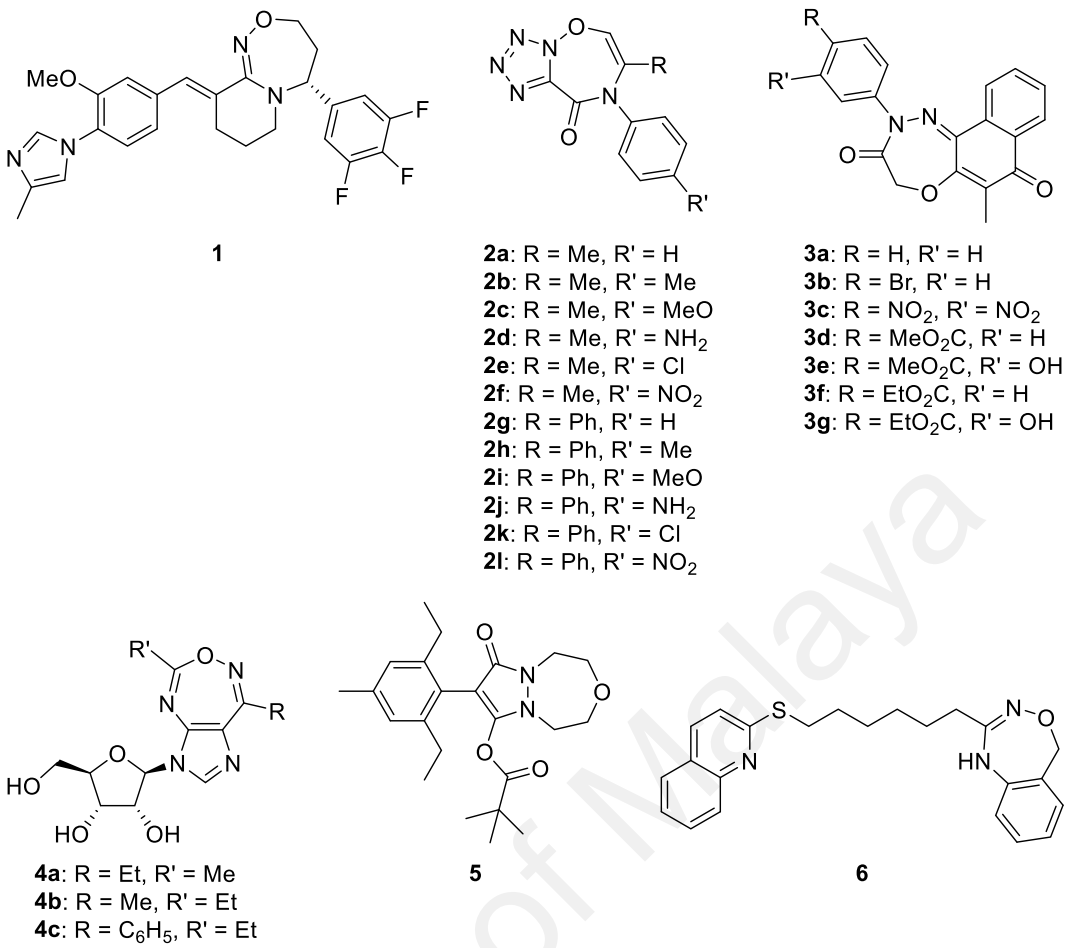
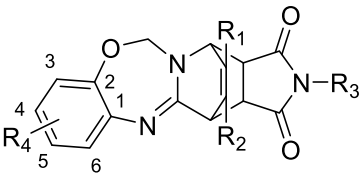
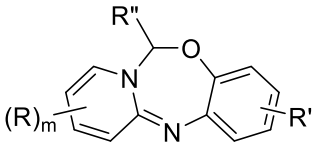


Figure 1.4. Oxadiazepine skeletons with biological activities.

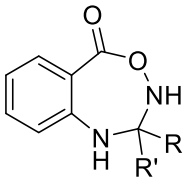
Similarly, benzoxadiazepines have also been reported to have some biological activities. For instance, compounds **7** and **8** as stimulant to the central nervous system (Petigara & Yale, 1974; Yale & Bristol, 1977; Yale & Petigara, 1974, 1979), compound **8** as muscle relaxant (Yale & Petigara, 1974, 1979), compound **9** as antibacterial (Reddy *et al.*, 1996) and compounds **10** and **11** as tranquilizer, anticonvulsant and pesticides (Singh *et al.*, 1995) (Figure 1.5).





8
(refer to Appendix for more details)

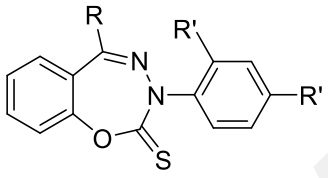
7a: R^1 = H, R^2 = Me, R^3 = C_6H_5, R^4 = 5-Br
7b: R^1 = Me, R^2 = H, R^3 = Me, R^4 = 3-Br
7c: R^1 = H, R^2 = H, R^3 = -CH_2-C_6H_5, R^4 = 6-Cl
7d: R^1 = Cl, R^2 = H, R^3 = -$(CH_2)_3CH_3$, R^4 = 5-$CH_2CH(CH_3)_2$
7e: R^1 = Me, R^2 = H, R^3 = -$CH(CH_3)_2$, R^4 = 5-C_6H_5
7f: R^1 = H, R^2 = Me, R^3 = Me, R^4 = 5-CF_3
7g: R^1 = -C_6H_5, R^2 = H, R^3 = -CH_2-C_6H_5, R^4 = 5-C_6H_5
7h: R^1 = H, R^2 = -CH_2-C_6H_5, R^3 = H , R^4 = 5-$SNO_2(CH_3)_2$
7i: R^1 = H, R^2 = H, R^3 = -$CH_2CH(CH_3)_2$, R^4 = H



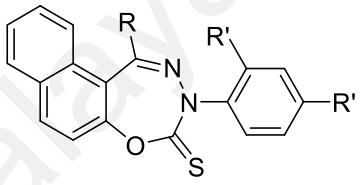
9a: R = R' = Me
9b: R = R' = -CH_2-C_6H_5
9c: R = Me, R' = C_6H_5

9d: R-R' =

9e: R-R' =



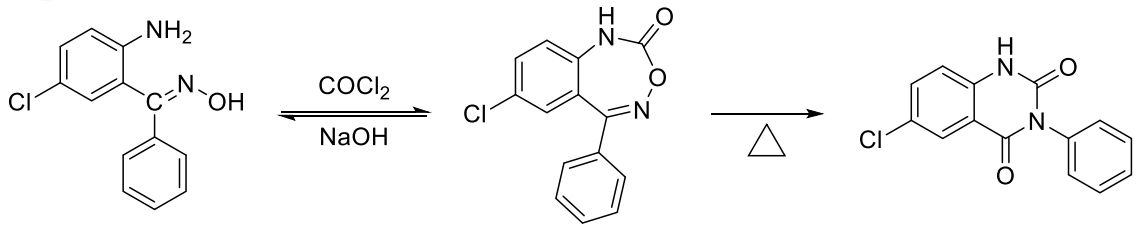
10a: R = H, R' = H
10b: R = H, R' = NO_2
10c: R = Me, R' = H
10d: R = Me, R' = NO_2



11a: R = H, R' = H
11b: R = H, R' = NO_2
10c: R = Me, R' = H

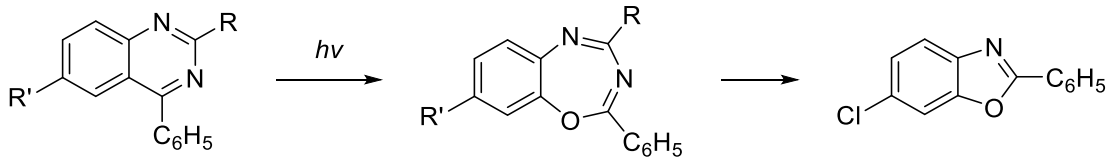
Figure 1.5. Benzoxadiazepine skeletons with biological activities.

In many cases, benzoxadiazepines were reported as intermediates in the synthesis of quinazoline **14** (Scheme 1.1) (Sulkowski & Childress, 1962), benzoxazole **17** (Scheme 1.2) (Field & Sternbach, 1968) or benzimidazole **21** (Scheme 1.3) (Mazurkiewicz, 1988). However, the synthesis of these heterocycles has scarcely been investigated in the literature.



12 **13** **14**

Scheme 1.1. Benzoxadiazepine intermediate for the synthesis of quinazoline **14**.

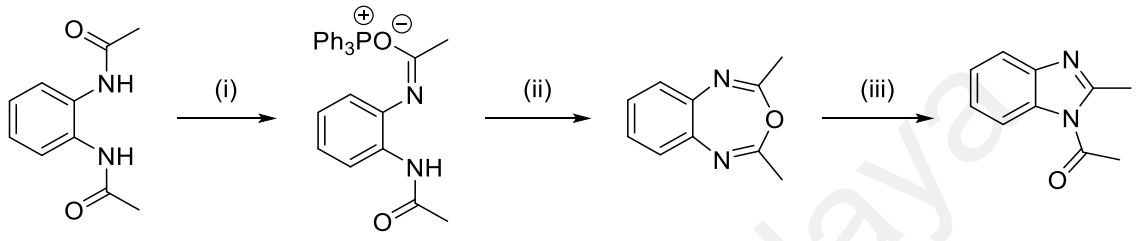


15a: R = Me, R' = Cl
15b: R = C_6H_5, R' = H
15c: R = H, R' = Cl

16a: R = Me, R' = Cl
16b: R = C_6H_5, R' = H
16c: R = H, R' = Cl

17

Scheme 1.2. Benzoxadiazepine intermediate for the synthesis of benzoxazole **17**.



18 **19** **20** **21**

Scheme 1.3. Benzoxadiazepine intermediate for the synthesis of benzimidazole **21**. Reagents and conditions: (i) Ph_3PBr_2, -HBr; (ii) -Ph_3PO, -HBr; (iii) HBr.

1.3 Problem Statement

Most reports for the synthetic method of benzoxadiazepines required multi-component reactions (Gadzhiev & Alekperov, 1982; Hassan *et al.*, 2010; Mei *et al.*, 2017). The tendency of functionally-substituted hydrazones to undergo intramolecular cyclization at the polar C=N bond of the hydrazone fragment is commonly used in the synthesis of five- (Alhadi *et al.*, 2015; Kim *et al.*, 1994; Lee *et al.*,2001; Sarshira *et al.*, 2016) and six-membered (Alkhathlan, 2003) heterocycles.

In 2015, the formation of simple five-membered 1,3,4-oxadiazoles via cyclization of substituted benzaldehyde acylhydrazones with a free hydroxy group at the *ortho* position were reported by Alhadi *et al*. Interestingly, the authors reported that in some cases, the formation of unusual seven-membered oxadiazepines was observed when the cyclization reactions of substituted benzaldehyde acylhydrazones were carried out at 50 – 60 °C in acetic anhydride/acetic acid solution. Encouraged by this unprecedented discovery of the seven-membered ring formation, we envisioned to develop a general and versatile

synthetic methodology for this class of seven-membered ring heterocycles. Among the benzoxadiazepine isomers, the benzo[*f*][1,3,4]oxadiazepines were chosen as the target skeletons for this research.

1.4 Objectives of Study

In this project, we aim to study the preference for the formation of seven-membered benzo[*f*][1,3,4]oxadiazepines in the cyclization reaction of *N*-(2-hydroxybenzoyl)hydrazones with a free hydroxyl group at the *ortho* position.

Thus, the objectives of this study are as follows:

1. To optimize the reaction condition for the formation of seven-membered benzo[*f*][1,3,4]oxadiazepines
2. To synthesize derivatives of seven-membered benzo[*f*][1,3,4]oxadiazepines
3. To study the influences of electron-donating and electron-withdrawing groups on both salicylic and benzylidene rings in the formation of benzo[*f*][1,3,4]oxadiazepines

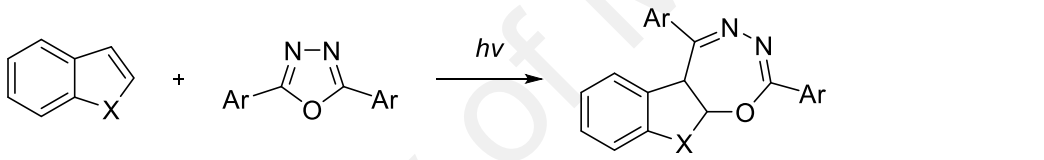
CHAPTER 2: LITERATURE REVIEW

2.1 Synthesis of Seven-membered Rings

Several studies have reported on the preparation of 1,3,4-oxadiazepine derivatives. However, some synthetic methods repeated indicated that the products formed were either isomeric five- or six-membered heterocycles.

2.1.1 1,3,4-Oxadiazepines

The earliest work for producing 1,3,4-oxadiazepines was reported by Oe *et al.* (1977), involved a photochemical reaction between indene **22a** or benzothiophene **22b** and 2,5-diaryl-1,3,4-oxadiazoles **23a-c** to produce the indenylphenyl-1,3,4-oxadiazepines **24a-c** or benzothiophenyl-1,3,4-oxadiazepine **24d** (Scheme 2.1).



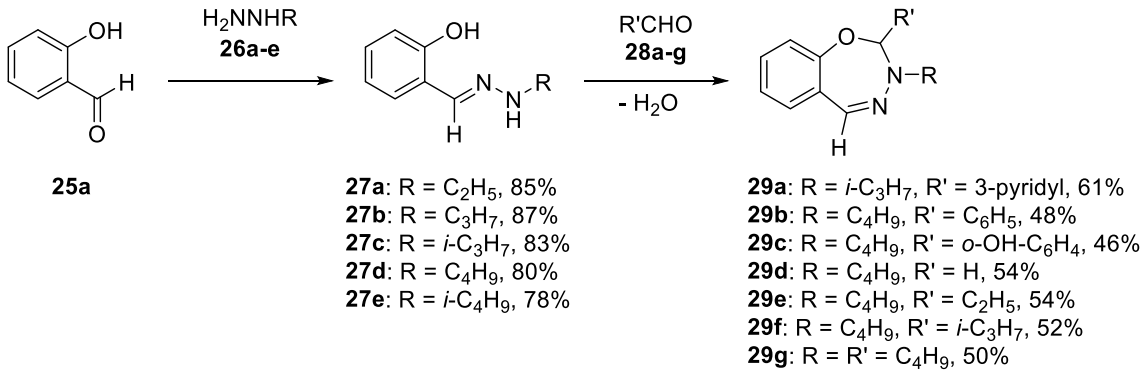
22a: X = C
22b: X = S

23a: Ar = C_6H_5
23b: Ar = *p*-tolyl
23c: Ar = C_6H_5 and *p*-tolyl

24a: X = C, Ar = C_6H_5, 31%
24b: X = C, Ar = *p*-tolyl, 27%
24c: X = C, Ar = C_6H_5 and *p*-tolyl, 40%
24d: X = S, Ar = C_6H_5, 69%

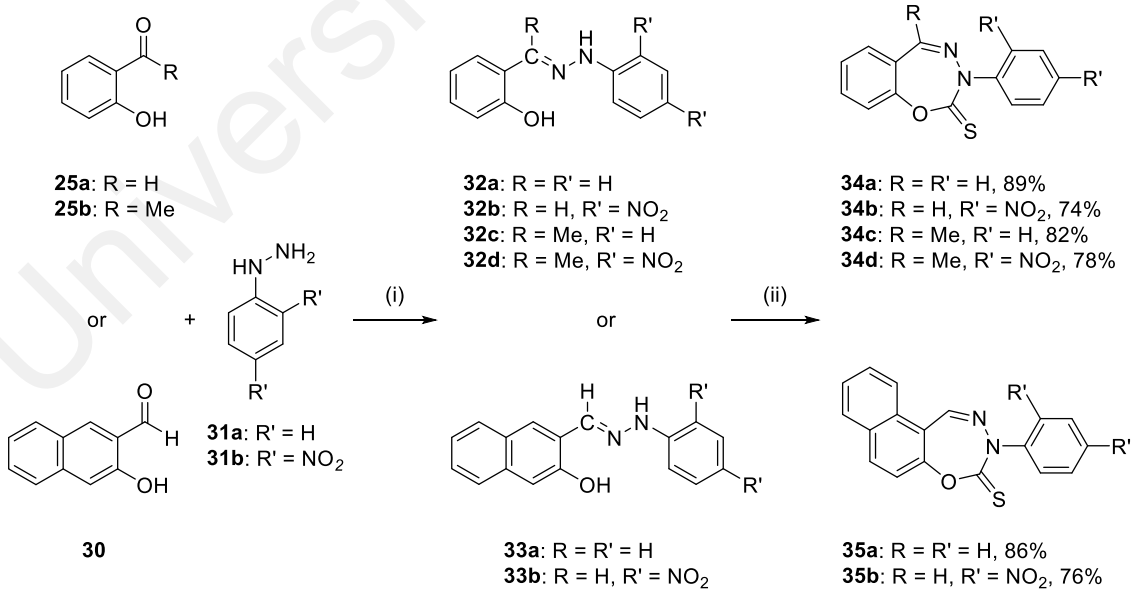
Scheme 2.1. Synthesis of indenyl- or benzothiophenyl-1,3,4-oxadiazepine **24a-d**.

Gadzhiev and Alekperov (1982) synthesized 2,3-disubstituted 6,7-benzo-2,3-dihydro-1,3,4-oxadiazepines **29a-g** by reacting salicylaldehyde **25a** with monoalkylated hydrazine **26a-e** to construct hydrazides **27a-e**, followed by condensation-cyclization reaction with aldehydes **28a-g** (Scheme 2.2).



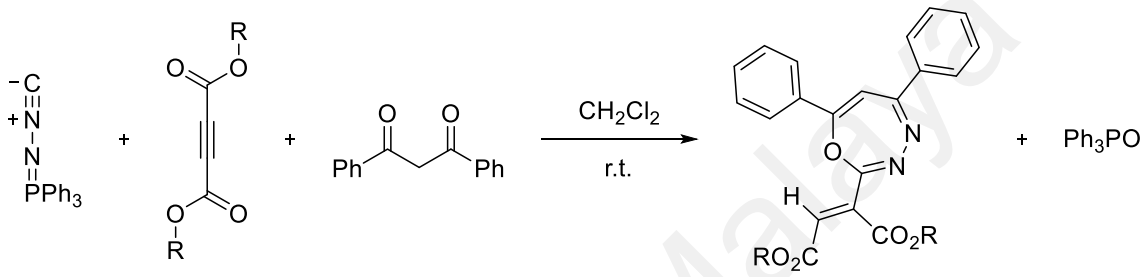
Scheme 2.2. Synthesis of 2,3-disubstituted 6,7-benzo-2,3-dihydro-1,3,4-oxadiazepines **29a-g**.

A series of compounds containing benzoxadiazepines **34a-d** and naphthoxadiazepines **35a-b** were prepared by Singh *et al.* (1995). Condensation of 2-hydroxyarylaldehydes **25a** and **30** or ketone **25b** with substituted arylhydrazines **31a-b** afforded substituted arylhydrazones **32a-d** and **33a-b**. Cyclization of **32a-d** and **33a-b** in the presence of thiophosgene and triethylamine gave 5-substitute-3-aryl-2*H*,3*H*-benzo-[1,2-*f*][1,3,4]-oxadiazepine-2-thiones **34a-d** and 5-substitute-3-aryl-2*H*,3*H*-naphtho-[1,2-*f*][1,3,4]-oxadiazepine-2-thiones **35a-b** as the desired product (Scheme 2.3).



Scheme 2.3. Synthesis of 5-substitute-3-aryl-2*H*,3*H*-benzo-[1,2-*f*][1,3,4]-oxadiazepine-2-thiones **34a-d** and 5-substitute-3-aryl-2*H*,3*H*-naphtho-[1,2-*f*][1,3,4]-oxadiazepine-2-thiones **35a-b**. Reagents and conditions: (i) 50% (*v/v*) H_2SO_4, reflux, 10 – 15 mins; (ii) Et_3N, $CSCl_2$, dry chloroform, ice bath.

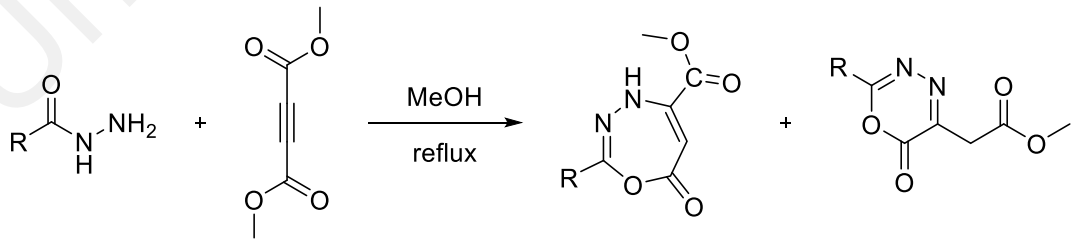
In the study by Souldozi *et al.* (2007), a multi-component reaction was utilized for the stereoselective synthesis of dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **39a-b**. Reactions of (*N*-isocyanimino)triphenylphosphorane **36** with dialkyl acetylenedicarboxylates **37a-b** in the presence of 1,3-diphenyl-1,3-propanedione **38** proceeded smoothly at room temperature to afford **39a-b** in high yields, where triphenylphosphine oxide **40** was produced as minor by-product (Scheme 2.4).



36 **37a**: R = Me; **37b**: R = Et **38** **39a**: R = Me, 92%; **39b**: R = Et, 91% **40**

Scheme 2.4. Synthesis of dialkyl (*Z*)-2-(5,7-diphenyl-1,3,4-oxadiazepin-2-yl)-2-butenedioates **39a-b**.

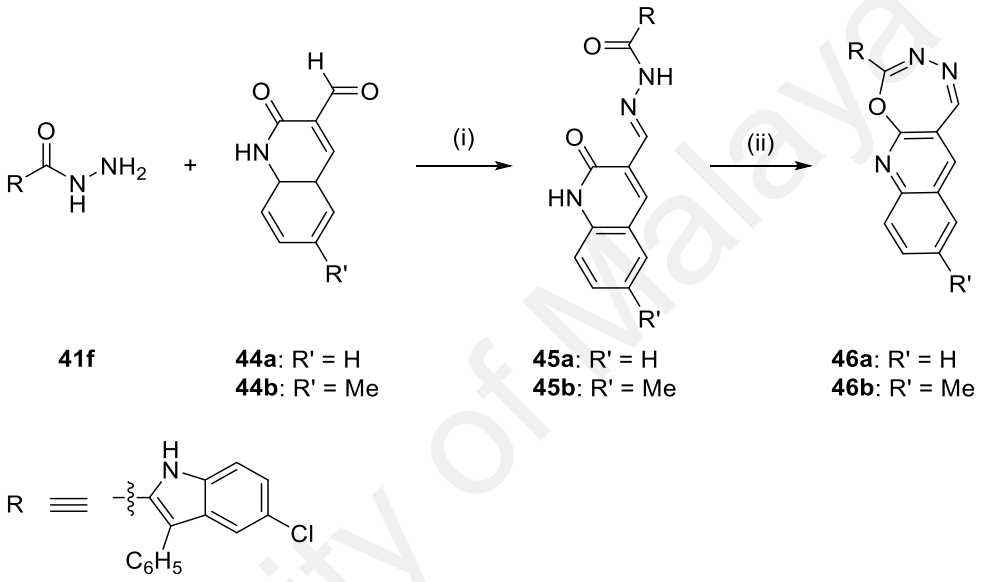
Hassan *et al.* (2008) reported the preparation of 7-oxa-2-substituted-4,7-dihydro-1,3,4-oxadiazepine-5-carboxylates **42a-e** from the condensation of substituted carbohydrazides **41a-e** with dimethyl but-2-ynedioate **37a** in refluxing methanol, where 1,3,4-oxadiazines **43** were produced as by-products (Scheme 2.5).



41a: R = phenyl; **41b**: R = 2-thienyl; **41c**: R = 2-furyl; **41d**: R = 2-pyridyl; **41e**: R = 2,3-dihydo-1*H*-indol-2-yl **37a** **42a**: R = phenyl, 65%; **42b**: R = 2-thienyl, 64%; **42c**: R = 2-furyl, 64%; **42d**: R = 2-pyridyl, 66%; **42e**: R = 2,3-dihydo-1*H*-indol-2-yl, 64% **43**

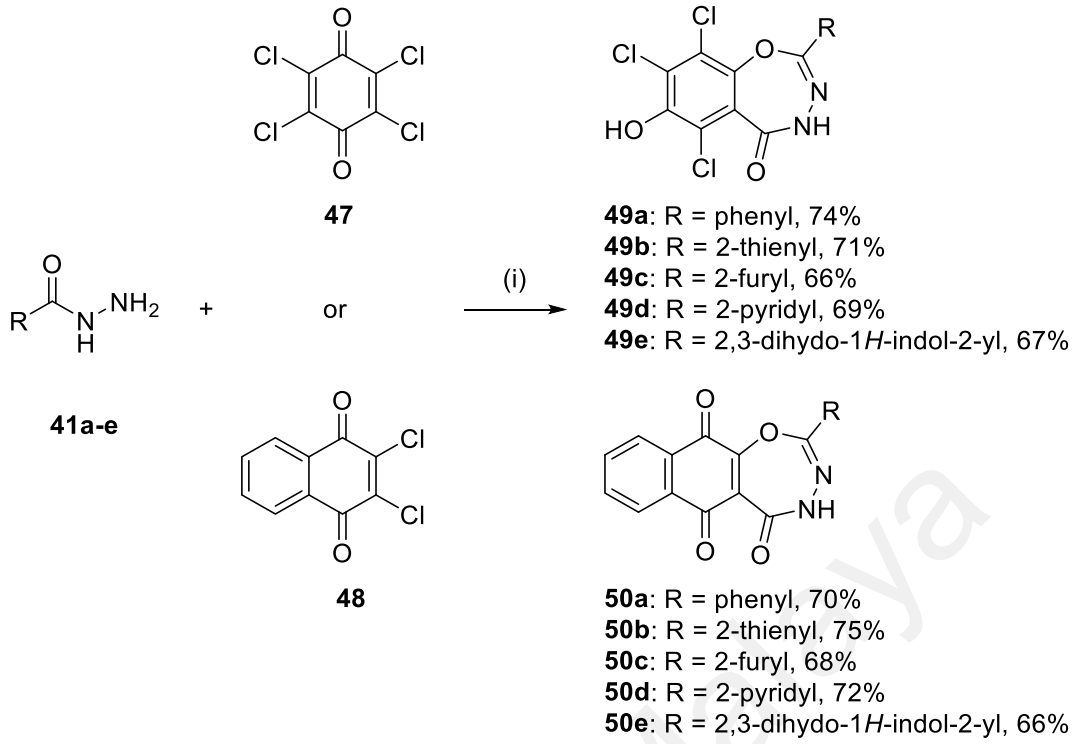
Scheme 2.5. Synthesis of 7-oxa-2-substituted-4,7-dihydro-1,3,4-oxadiazepine-5-carboxylate **42a-e**.

Basavarajaiah and Mruthyunjayaswamy (2009) showed the synthesis of hydrazones **45a-b** by condensation of 5-substituted-3-phenyl-2-carboxyhydrazide **41f** with substituted-3-formyl-2-hydroxy-quinolines **44a-b** in the presence of catalytic amount of glacial acetic acid. Compounds **45a-b**, on further reaction with concentrated H_2SO_4, gave 2-(5-chloro-3-phenyl-1*H*-inol-2yl)[1,3,4]oxadiazepino[7,6-*b*]quinolines **46a-b** (Scheme 2.6).



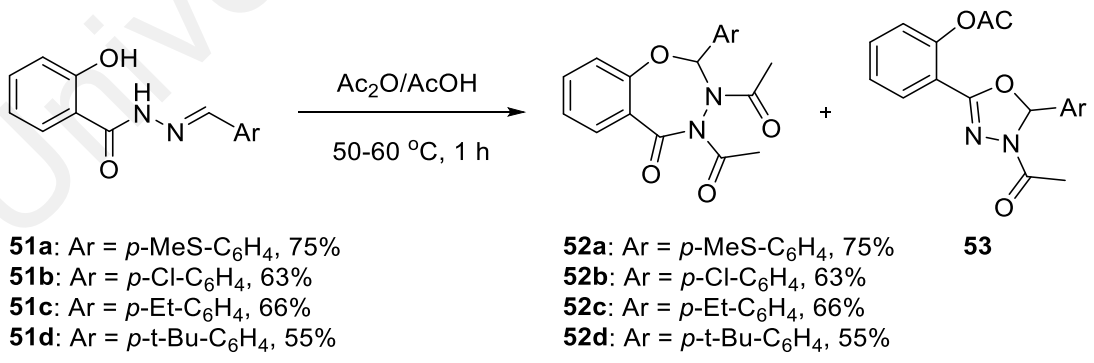
Scheme 2.6. Synthesis of 2-(5-chloro-3-phenyl-1*H*-inol-2yl)[1,3,4]oxadiazepino[7,6-*b*]quinoline **46a-b**. Reagents and conditions: (i) EtOH, AcOH, reflux, 7 – 8 h; (ii) Concentrated H_2SO_4.

With the aim to diversify the benzo-1,3,4-oxadiazepine scaffold, a series benzoxadiazepines **49a-e** and naphthoxadiazepines **50a-e** were prepared by Hassan *et al.* (2010) through the reaction of the substituted carbohydrazides **41a-e** with the corresponding chlorinated 1,4-benzoquinones **47** and 1,4-naphthoquinones **48** (Scheme 2.7).



Scheme 2.7. Synthesis of substituted benzoxadiazepine **49** and naphthoxadiazepine **50** derivatives. Reagents and conditions: (i) DMF, r.t.

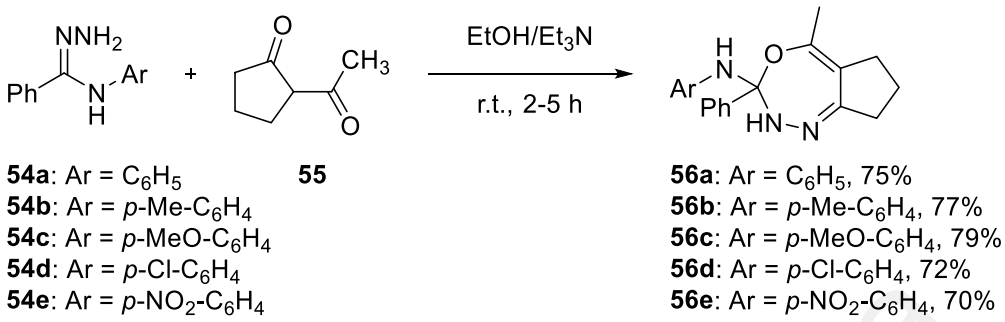
Alhadi *et al.* (2015) reported the cyclization of various benzaldehyde acylhydrazones **51a-d** in acetic anhydride to yield 1,3,4-oxadiazolines **53**. In some cases, the reaction that was carried out in acetic anhydride-acetic acid also gave 1,3,4-oxadiazepines **52a-d** (Scheme 2.8).



Scheme 2.8. Synthesis of 1,3,4-oxadiazepines **52a-d** and 1,3,4-oxadiazolines **53**.

In another example, Aly *et al.* (2017) produced the cyclopenta[*e*][1,3,4]-oxadiazepines **56a-e** through the reaction of amidrazones **54a-e** with 2-acetylcyclopentanone **55** in

absolute ethanol containing a few drops of triethylamine at room temperature (Scheme 2.9).

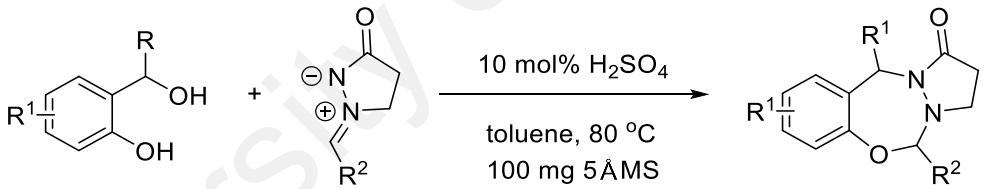


54a: Ar = C_6H_5 **55**
54b: Ar = *p*-Me-C_6H_4
54c: Ar = *p*-MeO-C_6H_4
54d: Ar = *p*-Cl-C_6H_4
54e: Ar = *p*-NO_2-C_6H_4

56a: Ar = C_6H_5, 75%
56b: Ar = *p*-Me-C_6H_4, 77%
56c: Ar = *p*-MeO-C_6H_4, 79%
56d: Ar = *p*-Cl-C_6H_4, 72%
56e: Ar = *p*-NO_2-C_6H_4, 70%

Scheme 2.9. Synthesis of cyclopenta[*e*][1,3,4]-oxadiazepines **56a-e**.

Recently, Mei *et al.* (2017) published their work on the construction of biologically important benzoxadiazepine scaffold **59** through Brønsted acid-catalyzed stereoselective [4+3] cycloadditions of *ortho*-hydroxybenzyl alcohols **57** with *N*,*N*'-cyclic azomethine imines **58** (Scheme 2.10).



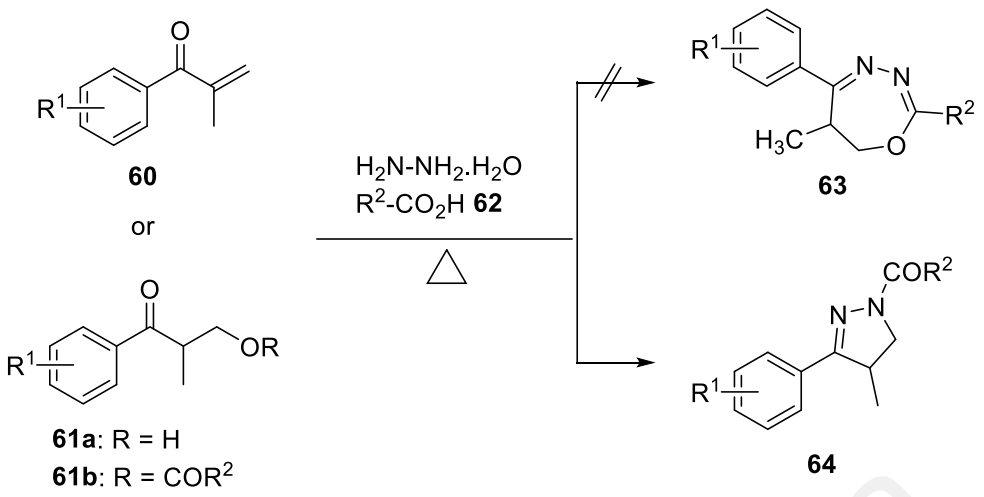
57 **58** **59**

Scheme 2.10. Synthesis of benzo-1,3,4-oxadiazepines **59**.

2.2 Attempted Preparation of 1,3,4-Oxadiazepines

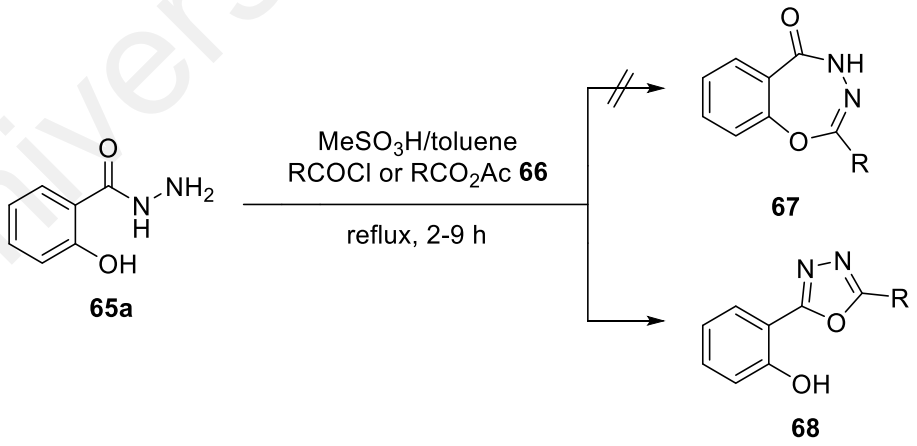
2.2.1 Five-membered Rings

In previous paper, Cignarella *et al.* (1984) reported the reaction of 3-hydroxy-2-methyl-1-aryl-propanones **61a** or their esters **61b**, as well as of 1-aryl-2-methyl-2-propen-1-ones **60**, with hydrazine hydrate in an appropriate carboxylic acid **62** as solvent to give 2,5,6-trisubstituted-6,7-dihydro-1,3,4-oxadiazepines **63**. In 1989, they determined these compounds to have the structures of 1-acyl/aroyl-3-aryl-4-methyl-4,5-dihydropyrazoles **64** (Cignarella *et al.*, 1989) (Scheme 2.11).



Scheme 2.11. Synthesis of 1-acyl/aroyl-3-aryl-4-methyl-4,5-dihydropyrazoles **64** instead of 2,5,6-trisubstituted-6,7-dihydro-1,3,4-oxadiazepines **63**.

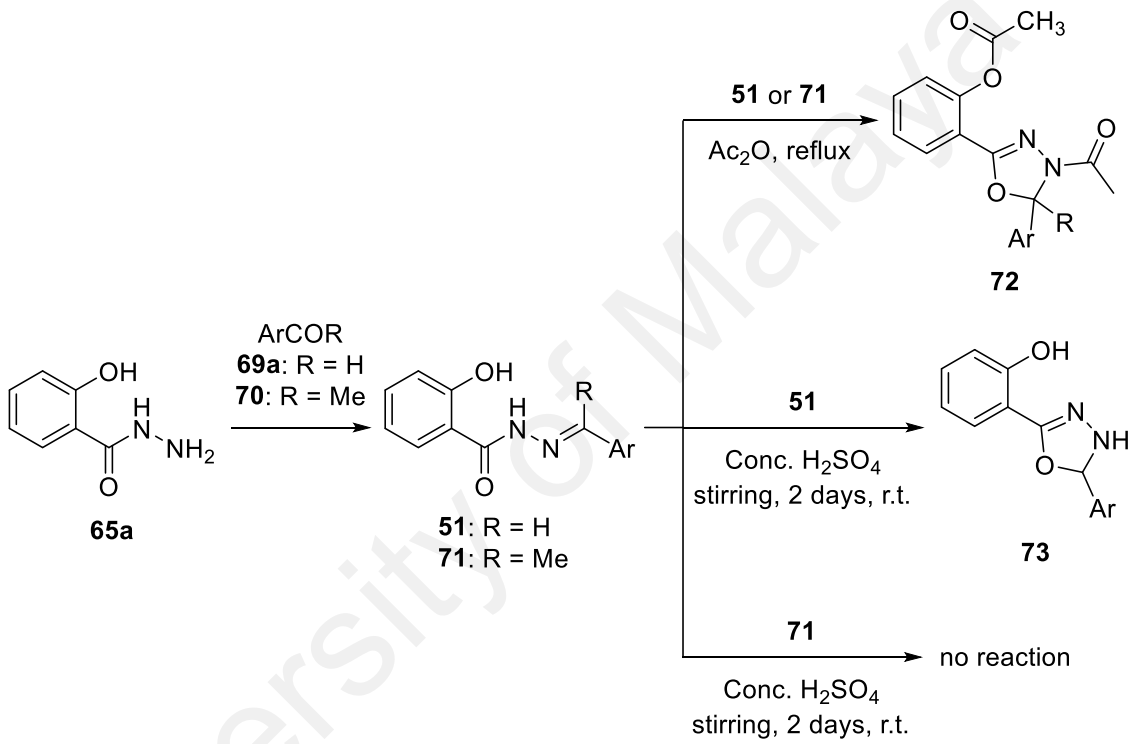
Lee *et al*. (1992) reported the preparation of 4,5-dihydro-5*H*-1,3,4-benzoxadiazepin-5-ones **67** based on the cyclocondensation reaction of 2-hydroxybenzohydrazide **65a** and acyl acetate or chlorides **66** in the presence of methanesulfonic acid. However, upon reinvestigation, Kim *et al.* (1994) and Lee *et al.* (2001) found one of the specific compounds produced to be 2-(2-hydroxyphenyl)-1,3,4-oxadiazole **68** rather than a 1,3,4-benzoxadiazepin-5-ones **67** as reported by Lee *et al*. (1992) (Scheme 2.12).



Scheme 2.12. Synthesis of 1,3,4-oxadiazoles **68** instead of 4,5-dihydro-5*H*-1,3,4-benzoxadiazepin-5-ones **67**.

Sarshira *et al.* (2016) prepared hydrazide-hydrazones **51** and **71** by acid-catalyzed condensation of 2-hydroxybenzohydrazide **65a** with the appropriate benzaldehyde **69a** or

acetophenone derivatives **70**. Treatment of **51** or **71** with acetic anhydride produced *N*-acetyl oxadiazole derivatives **72** in good yields. On the other hand, when **51** were stirred for 2 days in 10 mL of concentrated H_2SO_4 at room temperature, they underwent cyclization to give 2,3-dihydro-5-(2-hydroxyphenyl)-2-aryl-1,3,4-oxadiazoles **73**. It is noteworthy that treatment of **71** with concentrated H_2SO_4 and subsequent neutralization using 10% Na_2CO_3 resulted in formation of **65a** and **70** (Scheme 2.13).

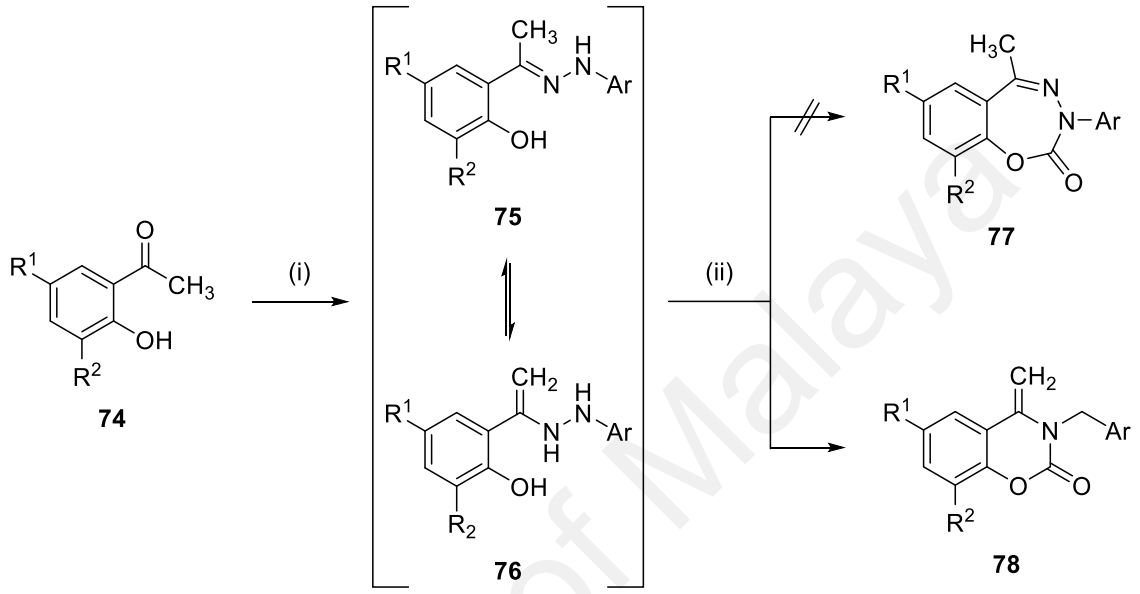


Scheme 2.13. Synthesis of 1,3,4-oxadiazole derivatives **72-73**.

2.2.2 Six-membered Rings

Alkhathlan (2003) reported the cyclization of hydrazone of 2-aminobenzophenone **75** into 4-methylene-1,3-benzoxazinones **78** with phosgene and paraformaldehyde. Compounds **75** was prepared from the reaction of substituted 2-hydroxyacetophenone **74** with aromatic hydrazines in ethanol with a few drops of acetic acid. The cyclization of **75** did not proceed to form a seven-membered benzoxadiazepine ring **77** in a similar manner to that previously reported for the cyclization of hydrazones of 2-aminobenzophenone into benzotriazepines with phosgene and paraformaldehyde

(Ishiwata & Shiokawa, 1970; Kohl *et al.*, 1974). The methyl group in hydrazone is involved in the cyclization step via the formation of enamine form of hydrazone **76** which reacts with thiophosgene to give **78** rather than **77**. A similar cyclization of the enol form of acetophenone has also been reported previously (Molina *et al.*, 1993) (Scheme 2.14).



Scheme 2.14. Synthesis of 4-methylene-1,3-benzoxazinones **78** instead of benzoxadiazepine **77**. Reagents and conditions: (i) Phenylhydrazine derivatives, EtOH, AcOH, reflux, 2 h; (ii) CH_2Cl_2, $CSCl_2$, Et_3N.

CHAPTER 3: METHODOLOGY

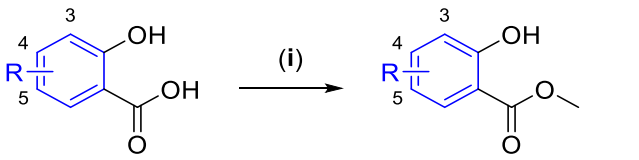
3.1 Materials and Methods

All chemicals and solvents were used as received without further purification unless stated. Analytical TLC was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F254). TLC visualization was accomplished under UV lamp (254 nm). Crude benzoxadiazepines were purified by silica gel (Merck) column chromatography using ethyl acetate/hexane as the eluent. NMR spectra were obtained using a JOEL ECA 400 (400 MHz) NMR spectrometer with TMS as the internal standard. All measurements were recorded in solution in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm relative to DMSO-d_6 or TMS. Data for ^1H NMR are reported as follows: chemical shift, multiplicity, coupling constant(s) and integration. All ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS (ESI) analyses were performed using Agilent 6500 Q-TOF (ESI) spectrometer with Agilent Zorbax C-18 column. Melting points were determined with a Stuart SMP30 melting point apparatus.

3.2 Experimental Procedure

3.2.1 General Procedure for the Synthesis of Methyl Salicylate Derivatives 80

The 2-hydroxybenzoic acid derivatives **79a-b** (5 mmol) were dissolved in MeOH (100 mL). Concentrated H_2SO_4 (98%, 2 mL) was added dropwise to the solution. The mixture was refluxed for 18 h at 80 °C. After the completion of the reaction, it was cooled to r.t. The solvent was removed under vacuum. Saturated $NaHCO_3$ solution was added to the reaction mixture until no evolution of gas was observed. The reaction mixture was extracted with chloroform. The organic layer was collected, dried over anhydrous Na_2SO_4 and evaporated under vacuum without further purification.

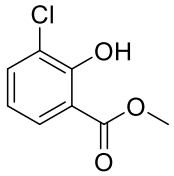


79a: R = 3-Cl
79b: R = 4-Cl
79c: R = 4-NO_2
79d: R = 5-NO_2

80a: R = 3-Cl, 81%
80b: R = 4-Cl, 98%
80c: R = 4-NO_2, 85%
80d: R = 5-NO_2, 93%

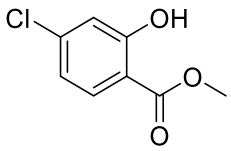
Scheme 3.1. Synthesis of methyl salicylate derivatives **80a-d** through esterification. Reagents and conditions: (i) MeOH, concentrated H_2SO_4, 80 °C, 18 h.

3.2.1.1 Methyl 3-chloro-2-hydroxybenzoate (80a)



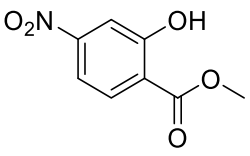
Brown solid; yield = 81%; m.p. 29 – 32 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.24 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 7.9 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 157.4, 135.9, 128.5, 122.3, 119.4, 113.7, 52.9. HRMS calcd. for $C_8H_7ClO_3$ $[M+H]^+$: 186.0084, found: 186.0093.

3.2.1.2 Methyl 4-chloro-2-hydroxybenzoate (80b)



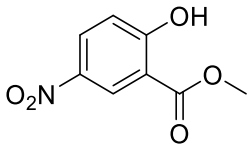
Brown oil; yield = 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.77 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 6.76 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 162.2, 141.5, 131.0, 120.0, 117.8, 111.1, 52.6. HRMS calcd. for $C_8H_7ClO_3$ $[M+H]^+$: 186.0084, found: 186.0089.

3.2.1.3 Methyl 2-hydroxy-4-nitrobenzoate (80c)



Red solid; yield = 85%; m.p. 98 – 101 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 8.6, 2.2 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 160.3, 150.7, 131.9, 121.8, 112.4, 111.9, 52.5. HRMS calcd. for $C_8H_7NO_5$ $[M+H]^+$: 197.0324, found: 197.0302.

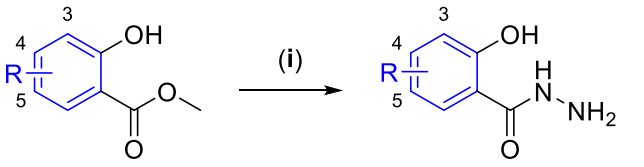
3.2.1.4 Methyl 2-hydroxy-5-nitrobenzoate (80d)



Pale yellow solid; yield = 93%; m.p. 115 – 117 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (d, J = 2.9 Hz, 1H), 8.27 (dd, J = 9.0, 2.9 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 116.2, 164.5, 138.9, 129.6, 126.9, 118.7, 115.3, 52.7. HRMS calcd. for $C_8H_7NO_5$ $[M+H]^+$: 197.0324, found: 197.0302.

3.2.2 General Procedure for the Synthesis of *N*-(2-Hydroxybenzoyl)hydrazides 65

The corresponding **80a-j** (2 mmol) and hydrazine hydrate (10 mmol) were dissolved in EtOH (20 mL). The mixture was refluxed for 5 h at 80 °C. After the completion of the reaction, it was cooled to r.t. The solvent was removed under vacuum, resulting the formation of the desired compounds without further purification.

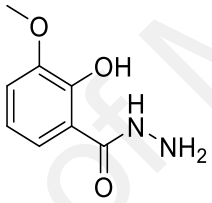


80a: R = 3-Cl, 81%
80b: R = 4-Cl, 98%
80c: R = 4-NO_2, 85%
80d: R = 5-NO_2, 93%
80e: R = 3-MeO
80f: R = 3-NO_2
80g: R = 4-Me
80h: R = 4-MeO
80i: R = 5-Me
80j: R = 5-MeO

65b: R = 3-MeO, 95%
65c: R = 3-Cl, 99%
65d: R = 3-NO_2, 99%
65e: R = 4-Me, 96%
65f: R = 4-MeO, 92%
65g: R = 4-Cl, 92%
65h: R = 4-NO_2, 95%
65i: R = 5-Me, 99%
65j: R = 5-MeO, 87%
65k: R = 5-NO_2, 99%

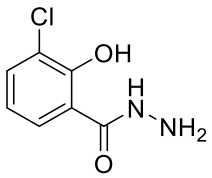
Scheme 3.2. Synthesis of *N*-(2-hydroxybenzoyl)hydrazides **65** through hydrazination. Reagents and conditions: (i) $N_2H_4.H_2O$ and EtOH, 80 °C, 5 h.

3.2.2.1 2-Hydroxy-3-methoxybenzohydrazide (65b)



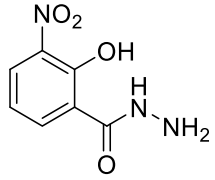
Dark brown crystal; yield = 95%; m.p. 136 – 140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.49 (t, J = 7.9 Hz, 1H), 5.61 (br s), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3, 150.3, 148.4, 118.0, 117.9, 115.1, 114.1, 55.7. HRMS calcd. for $C_8H_{10}N_2O_3$ $[M+H]^+$: 182.0691, found: 182.0703.

3.2.2.2 3-Chloro-2-hydroxybenzohydrazide (65c)



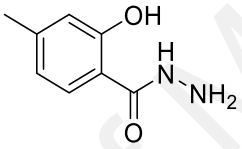
Dark brown solid; yield = 99%; m.p. 163 – 168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (dd, J = 7.9, 1.1 Hz, 1H), 7.55 (dd, J = 8.2, 1.4 Hz, 1H), 6.86 (t, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 156.4, 133.4, 125.3, 121.1, 118.7, 115.2. HRMS calcd. for $C_7H_7ClN_2O_2$ $[M+H]^+$: 186.0196, found: 186.0195.

3.2.2.3 2-Hydroxy-3-nitrobenzohydrazide (65d)



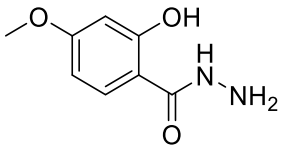
Brown powder; yield = 99%; m.p. 182 – 186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 6.52 (t, J = 7.9 Hz, 1H), 4.84 (br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.2, 164.6, 140.0, 134.8, 128.8, 123.6, 107.8. HRMS calcd. for $C_7H_7N_3O_4$ $[M+H]^+$: 197.0437, found: 197.0454.

3.2.2.4 2-Hydroxy-4-methylbenzohydrazide (65e)



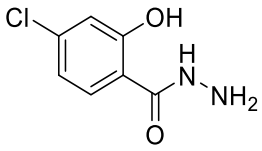
Yellow solid; yield = 96%; m.p. 165 – 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, J = 8.2 Hz, 1H), 6.69 (s, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.54 (br s), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.0, 160.4, 143.5, 127.2, 119.1, 117.7, 112.1, 21.1. HRMS calcd. for $C_8H_{10}N_2O_2$ $[M+H]^+$: 166.0742, found: 166.0742.

3.2.2.5 2-Hydroxy-4-methoxybenzohydrazide (65f)



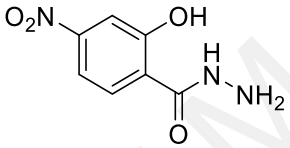
Brown solid; yield = 92%; m.p. 165 – 168 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (d, J = 8.6 Hz, 1H), 6.51-6.36 (m, 2H), 4.58 (br s), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 163.4, 162.2, 128.1, 106.8, 106.1, 101.2, 55.3. HRMS calcd. for $C_8H_{10}N_2O_3$ $[M+H]^+$: 182.0691, found: 182.0695.

3.2.2.6 4-Chloro-2-hydroxybenzohydrazide (65g)



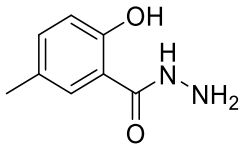
Brown solid; yield = 92%; m.p. 208 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 1.8 Hz, 1H), 6.53 (dd, J = 8.4, 2.0 Hz, 1H), 5.70 (br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 162.1, 136.7, 129.7, 117.4, 116.9, 115.2. HRMS calcd. for $C_7H_7ClN_2O_2$ $[M+H]^+$: 186.0196, found:186.0208.

3.2.2.7 2-Hydroxy-4-nitrobenzohydrazide (65h)



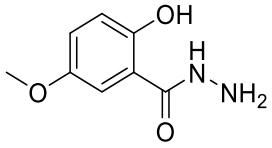
Red crystal; yield = 95%; m.p. 166 – 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 6.91 (dd, J = 8.6, 2.3 Hz, 1H), 5.57 (br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 166.0, 150.0, 129.8, 124.1, 114.8, 102.8. HRMS calcd. for $C_7H_7N_3O_4$ $[M+H]^+$: 197.0437, found: 197.0450.

3.2.2.8 2-Hydroxy-5-methylbenzohydrazide (65i)



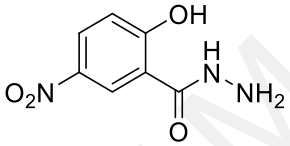
Pale brown powder; yield = 99%; m.p. 119 – 122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.8, 157.5, 134.0, 127.3, 127.0, 117.1, 114.2, 20.1. HRMS calcd. for $C_8H_{10}N_2O_2$ $[M+H]^+$: 166.0742, found: 166.0743.

3.2.2.9 2-Hydroxy-5-methoxybenzohydrazide (65j)



Brown solid; yield = 87%; m.p. 150 – 155 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (d, J = 2.9 Hz, 1H), 6.98 (dd, J = 9.0, 2.9 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 153.6, 151.5, 120.6, 118.1, 114.1, 110.5, 55.6. HRMS calcd. for $C_8H_{10}N_2O_3$ $[M+H]^+$: 182.0691, found: 182.0693.

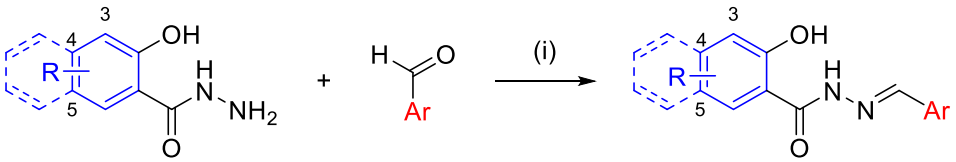
3.2.2.10 2-Hydroxy-5-nitrobenzohydrazide (65k)



Brown solid; yield = 99%; m.p. 184 – 188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (d, J = 3.2 Hz, 1H), 7.78 (dd, J = 9.5, 3.2 Hz, 1H), 6.26 (d, J = 9.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.7, 166.0, 130.0, 128.0, 127.0, 122.2, 117.7. HRMS calcd. for $C_7H_7N_3O_4$ $[M+H]^+$: 197.0437, found: 197.0443.

3.2.3 General Procedure for the Synthesis of *N*-(2-Hydroxybenzoyl)hydrazones 51

The corresponding **65b-k** (2.00 mmol) and benzaldehyde derivatives **69a-i** (2.00 mmol) were dissolved in EtOH (20 mL). The mixture was refluxed for 8 h at 80 °C. After the completion of the reaction, the reaction mixture was cooled to r.t. The solvent was removed under vacuum. The resulting product was washed with small amount of cold ethanol. Further purification of the crude product was carried out by recrystallization in hot ethanol to afford the hydrazones. For compounds **51i**, **51m** and **51q**, *L*-(+)-tartaric acid (45 mol %) was used as catalyst.



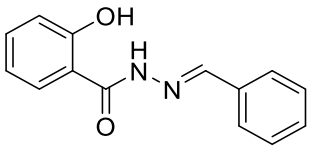
65a: R = H
65b: R = 3-MeO, 95%
65c: R = 3-Cl, 99%
65d: R = 3-NO_2, 99%
65e: R = 4-Me, 96%
65f: R = 4-MeO, 92%
65g: R = 4-Cl, 92%
65h: R = 4-NO_2, 95%
65i: R = 5-Me, 99%
65j: R = 5-MeO, 87%
65k: R = 5-NO_2, 99%
65l: R = 3-Me
65m: R = 2-naphthyl

69a: Ar = C_6H_5
69b: Ar = *p*-MeO-C_6H_4
69c: Ar = *p*-MeS-C_6H_4
69d: Ar = *p*-Cl-C_6H_4
69e: Ar = *p*-MeO_2C-C_6H_4
69f: Ar = *p*-CN-C_6H_4
69g: Ar = *p*-NO_2-C_6H_4
69h: Ar = 2-naphthyl
69i: Ar = *m*-NO_2-C_6H_4

51a: R = H, Ar = *p*-MeS-C_6H_4, 85%
51b: R = H, Ar = *p*-Cl-C_6H_4, 87%
51e: R = H, Ar = C_6H_5, 73%
51f: R = 3-Me, Ar = C_6H_5, 98%
51g: R = 3-MeO, Ar = C_6H_5, 96%
51h: R = 3-Cl, Ar = C_6H_5, 40%
51i: R = 3-NO_2, Ar = C_6H_5, 62%
51j: R = 4-Me, Ar = C_6H_5, 80%
51k: R = 4-MeO, Ar = C_6H_5, 82%
51l: R = 4-Cl, Ar = C_6H_5, 90%
51m: R = 4-NO_2, Ar = C_6H_5, 70%
51n: R = 2-naphthyl, Ar = C_6H_5, 73%
51o: R = 5-Me, Ar = C_6H_5, 98%
51p: R = 5-MeO, Ar = C_6H_5, 86%
51q: R = 5-NO_2, Ar = C_6H_5, 64%
51r: R = H, Ar = *p*-MeO-C_6H_4, 90%
51s: R = H, Ar = *p*-MeO_2C-C_6H_4, 91%
51t: R = H, Ar = *p*-CN-C_6H_4, 93%
51u: R = H, Ar = *p*-NO_2-C_6H_4, 94%
51v: R = H, Ar = 2-naphthyl, 92%
51w: R = H, Ar = *m*-NO_2-C_6H_4, 89%
51x: R = 4-Cl, Ar = *p*-MeO-C_6H_4, 76%
51y: R = 4-Cl, Ar = *p*-MeS-C_6H_4, 62%
51z: R = 4-Cl, Ar = *p*-Cl-C_6H_4, 71%
51aa: R = 4-Cl, Ar = *p*-MeO_2C-C_6H_4, 91%
51ab: R = 4-Cl, Ar = *p*-CN-C_6H_4, 76%
51ac: R = 4-Cl, Ar = *p*-NO_2-C_6H_4, 88%
51ad: R = 4-Cl, Ar = 2-naphthyl, 88%
51ae: R = 4-Me, Ar = *p*-MeO-C_6H_4, 50%
51af: R = 4-Me, Ar = *p*-MeS-C_6H_4, 57%
51ag: R = 4-Me, Ar = *p*-Cl-C_6H_4, 57%
51ah: R = 4-Me, Ar = *p*-NO_2-C_6H_4, 80%
51ai: R = 4-Me, Ar = 2-naphthyl, 84%
51aj: R = 2-naphthyl, Ar = *p*-MeO-C_6H_4, 84%
51ak: R = 2-naphthyl, Ar = *p*-MeS-C_6H_4, 85%
51al: R = 2-naphthyl, Ar = *p*-Cl-C_6H_4, 89%
51am: R = 2-naphthyl, Ar = *p*-NO_2-C_6H_4, 93%
51an: R = 2-naphthyl, R' = 2-naphthyl, 90%

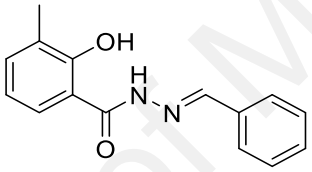
Scheme 3.3. Synthesis of *N*-(2-hydroxybenzoyl)hydrazones **51** through condensation. Reagents and conditions: (i) Absolute EtOH and *L*-(+)-tartaric acid (only for the synthesis of **51i, 51m** and **51q**), 80 °C, 8 h.

3.2.3.1 *N*'-benzylidene-2-hydroxybenzohydrazide (51e)



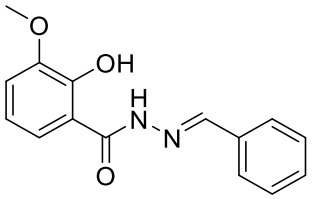
White powder; yield = 73%; m.p. 242 – 246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 2H), 8.47 (s, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.83-7.66 (m, 2H), 7.59-7.36 (m, 4H), 7.10-6.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 159.1, 148.7, 134.1, 133.9, 130.3, 128.9, 128.6, 127.3, 119.0, 117.3, 115.9. HRMS calcd. for $C_{14}H_{12}N_2O_2$ $[M+H]^+$: 240.0899, found: 240.0920.

3.2.3.2 *N*'-benzylidene-2-hydroxy-3-methylbenzohydrazide (51f)



White crystal; yield = 98%; m.p. 167 – 169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66 (s, 1H), 12.04 (s, 1H), 8.52 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.80-7.67 (m, 2H), 7.59-7.42 (m, 3H), 7.37 (d, J = 7.2 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 159.5, 149.4, 135.1, 134.0, 130.5, 128.9, 127.3, 126.3, 124.8, 118.0, 112.8, 15.5. HRMS calcd. for $C_{15}H_{14}N_2O_2$ $[M+H]^+$: 254.1055, found: 254.1078.

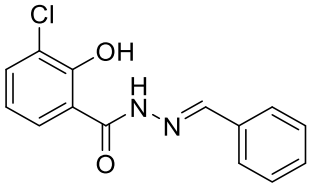
3.2.3.3 *N*'-benzylidene-2-hydroxy-3-methoxybenzohydrazide (51g)



Brown powder; yield = 96%; m.p. 103 – 107 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H), 11.82 (s, 1H), 8.47 (s, 1H), 7.82-7.69 (m, 2H), 7.53-7.41 (m, 4H), 7.16 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 8.2 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6):

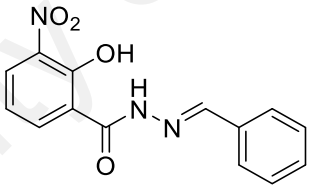
δ 165.5, 149.8, 149.0, 148.5, 134.1, 130.4, 129.0, 127.3, 119.3, 118.5, 115.6, 115.5, 56.0. HRMS calcd. for $C_{15}H_{14}N_2O_3$ $[M+H]^+$: 270.1004, found: 270.1007.

3.2.3.4 *N*'-benzylidene-3-chloro-2-hydroxybenzohydrazide (51h)



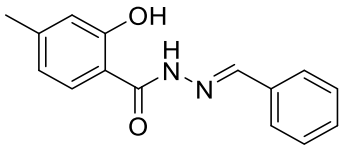
Brown solid; yield = 40%; m.p. 161 –165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (s, 1H), 12.17 (s, 1H), 8.52 (s, 1H), 7.93 (dd, J = 8.2, 1.4 Hz, 1H), 7.82-7.71 (m, 2H), 7.66 (dd, J = 7.8, 0.9 Hz, 1H), 7.56-7.43 (m, 3H), 7.00 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.7, 156.4, 150.0, 134.2, 133.8, 130.7, 129.0, 127.4, 126.4, 121.4, 119.2, 115.9. HRMS calcd. for $C_{14}H_{11}ClN_2O_2$ $[M+H]^+$: 274.0509, found: 274.0529.

3.2.3.5 *N*'-benzylidene-2-hydroxy-3-nitrobenzohydrazide (51i)



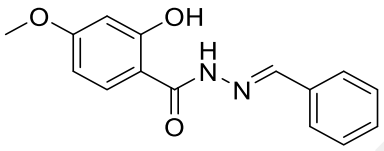
Yellow powder; yield = 62%; m.p. 203 –208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.44 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.81-7.69 (m, 2H), 7.52-7.40 (m, 3H), 6.95 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 156.3, 149.3, 138.8, 134.0, 133.9, 130.5, 129.1, 128.9, 128.8, 127.4, 120.2, 116.1. HRMS calcd. for $C_{14}H_{11}N_3O_4$ $[M+H]^+$: 285.0750, found: 285.0764.

3.2.3.6 *N*'-benzylidene-2-hydroxy-4-methylbenzohydrazide (51j)



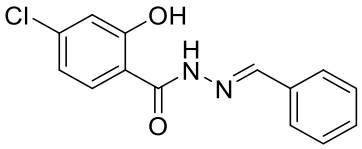
White crystal; yield = 80%; m.p. 226 – 229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.02 (s, 1H), 11.82 (s, 1H), 8.47 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.79-7.69 (m, 2H), 7.52-7.40 (m, 3H), 6.83-6.74 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.1, 159.6, 148.6, 144.7, 134.2, 130.3, 128.9, 128.2, 127.3, 120.0, 117.6, 112.5, 21.2. HRMS calcd. for $C_{15}H_{14}N_2O_2$ $[M+H]^+$: 254.1055, found: 254.1063.

3.2.3.7 *N*'-benzylidene-2-hydroxy-4-methoxybenzohydrazide (51k)



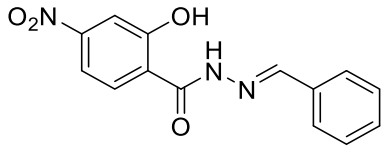
Brown crystal; yield = 82%; m.p. 205 – 209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.51 (s, 1H), 11.79 (s, 1H), 8.46 (s, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.82-7.68 (m, 2H), 7.54-7.42 (m, 3H), 6.56 (dd, J = 9.1, 2.7 Hz, 1H), 6.50 (d, J = 2.7 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 164.0, 162.4, 148.4, 134.2, 130.3, 129.5, 128.9, 127.2, 107.4, 106.5, 101.4, 55.5. HRMS calcd. for $C_{15}H_{14}N_2O_3$ $[M+H]^+$: 270.1004, found: 270.1012.

3.2.3.8 *N*'-benzylidene-4-chloro-2-hydroxybenzohydrazide (51l)



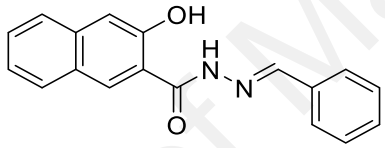
White crystal; yield = 90%; m.p. 261 – 264 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (s, 1H), 11.83 (s, 1H), 8.45 (s, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.80-7.69 (m, 2H), 7.51-7.41 (m, 3H), 7.09-7.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 159.5, 148.9, 137.6, 134.1, 130.5, 130.4, 128.9, 127.3, 119.2, 116.9, 115.7. HRMS calcd. for $C_{14}H_{11}ClN_2O_2$ $[M+H]^+$: 274.0509, found: 274.0527.

3.2.3.9 *N*'-benzylidene-2-hydroxy-4-nitrobenzohydrazide (51m)



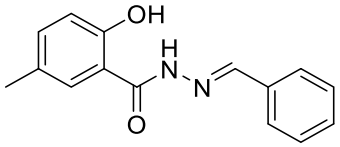
Yellow powder; yield = 70%; m.p. 340 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.30 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 7.7 Hz, 2H), 7.52-7.33 (m, 3H), 7.16 (d, J = 1.8 Hz, 1H), 6.95 (dd, J = 8.6, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 164.3, 150.6, 146.4, 135.0, 130.5, 129.6, 128.7, 127.1, 123.5, 115.2, 102.9. HRMS calcd. for $C_{14}H_{11}N_3O_4$ $[M+H]^+$: 285.0750, found: 285.0763.

3.2.3.10 *N*'-benzylidene-3-hydroxy-2-naphthohydrazide (51n)



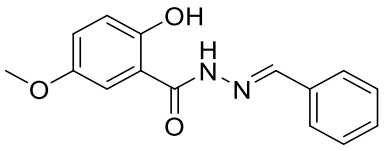
Brown crystal; yield = 73%; m.p. 227 – 230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H), 11.32 (s, 1H), 8.47 (s, 1H), 8.47 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.82-7.69 (m, 3H), 7.62-7.44 (m, 4H), 7.42-7.32 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 154.0, 148.5, 135.8, 134.2, 130.3, 128.9, 128.7, 128.3, 127.3, 126.8, 125.9, 123.8, 120.5, 110.6. HRMS calcd. for $C_{18}H_{14}N_2O_2$ $[M+H]^+$: 290.1055, found: 290.1076.

3.2.3.11 *N*'-benzylidene-2-hydroxy-5-methylbenzohydrazide (51o)



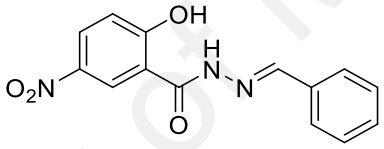
Pale brown crystal; yield = 98%; m.p. 207 – 209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 11.64 (s, 1H), 8.46 (s, 1H), 7.84-7.73 (m, 2H), 7.71 (s, 1H), 7.57-7.39 (m, 3H), 7.25 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 156.9, 148.6, 134.6, 134.2, 130.3, 128.9, 128.4, 127.7, 127.3 117.2, 115.4, 20.1. HRMS calcd. for $C_{15}H_{14}N_2O_2$ $[M+H]^+$: 254.1055, found: 254.1079.

3.2.3.12 *N*'-benzylidene-2-hydroxy-5-methoxybenzohydrazide (51p)



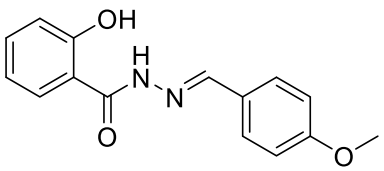
Brown crystal; yield = 86%; m.p. 223 – 228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.83 (s, 1H), 11.39 (s, 1H), 8.47 (s, 1H), 7.90-7.62 (m, 2H), 7.58-7.45 (m, 3H), 7.44 (d, J = 2.7 Hz, 1H), 7.08 (dd, J = 8.8, 2.9 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 152.9, 151.7, 148.7, 134.1, 130.3, 128.9, 127.3, 120.7, 118.2, 115.9, 112.2, 55.7. HRMS calcd. for $C_{15}H_{14}N_2O_3$ $[M+H]^+$: 270.1004, found: 270.1028.

3.2.3.13 *N*'-benzylidene-2-hydroxy-5-nitrobenzohydrazide (51q)



Pale brown solid; yield = 64%; m.p. 252 – 255 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.35 (s, 1H), 8.76 (d, J = 2.7 Hz, 1H), 8.45 (s, 1H), 8.24 (dd, J = 9.1, 2.7 Hz, 1H), 7.82-7.71 (m, 2H), 7.51-7.43 (m, 3H), 7.08 (d, J = 9.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.3, 162.5, 149.1, 138.5, 134.0, 130.4, 128.9, 128.5, 127.3, 125.9, 118.6, 117.7. HRMS calcd. for $C_{14}H_{11}N_3O_4$ $[M+H]^+$: 285.0750, found: 285.0763.

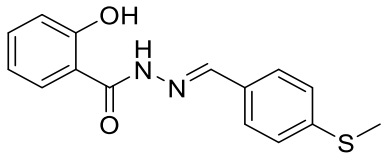
3.2.3.14 2-Hydroxy-*N*'-(4-methoxybenzylidene)benzohydrazide (51r)



White crystal; yield = 90%; m.p. 224 – 226 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 11.76 (s, 1H), 8.41 (s, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 7.00-6.87 (m, 2H), 3.81 (s, 3H).

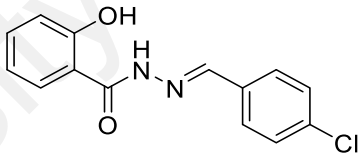
^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 161.0, 159.2, 148.7, 133.8, 128.9, 128.4, 126.6, 118.9, 117.3, 115.8, 114.4, 55.3. HRMS calcd. for $C_{15}H_{14}N_2O_3$ $[M+H]^+$: 270.1004, found: 270.1028.

3.2.3.15 2-Hydroxy-*N*'-(4-(methylthio)benzylidene)benzohydrazide (51a)



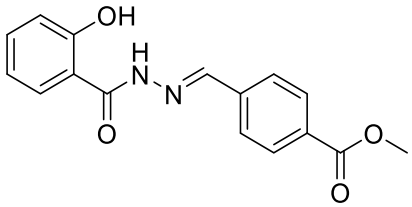
White powder; yield = 85%; m.p. 245 – 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H), 8.41 (s, 1H), 7.88 (dd, J = 8.0, 1.6 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.48-7.40 (m, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.00-6.92 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 159.0, 148.3, 141.3, 133.8, 130.5, 128.6, 127.7, 125.6, 119.0, 117.3, 115.9, 14.2. HRMS calcd. for $C_{15}H_{14}N_2O_2S$ $[M+H]^+$: 286.0776, found: 286.0781.

3.2.3.16 *N*'-(4-chlorobenzylidene)-2-hydroxybenzohydrazide (51b)



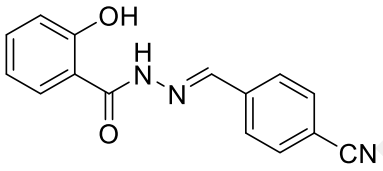
White powder; yield = 87%; m.p. 262 – 266 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 11.79 (s, 1H), 8.45 (s, 1H), 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.49-7.37 (m, 1H), 7.08-6.89 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 158.9, 147.3, 134.7, 133.9, 133.1, 129.0, 128.9, 128.7, 119.1, 117.3, 116.1. HRMS calcd. for $C_{14}H_{11}ClN_2O_2$ $[M+H]^+$: 274.0509, found: 274.0510.

3.2.3.17 Methyl 4-((2-(2-hydroxybenzoyl)hydrazono)methyl)benzoate (51s)



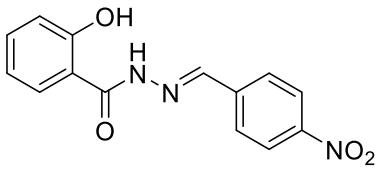
Pale yellow solid; yield = 91%; m.p. 262 – 264 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (s, 1H), 11.69 (s, 1H), 8.51 (s, 1H), 8.03 (d, J = 8.2 Hz, 2H), 7.88 (m, 3H), 7.45 (t, J = 7.7 Hz, 1H), 7.08-6.89 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 164.8, 158.8, 147.2, 138.6, 134.0, 130.6, 129.7, 128.9, 127.4, 119.1, 117.3, 116.2, 52.3. HRMS calcd. for $C_{16}H_{14}N_2O_4$ $[M+H]^+$: 298.0954, found: 298.0958.

3.2.3.18 *N*'-(4-cyanobenzylidene)-2-hydroxybenzohydrazide (51t)



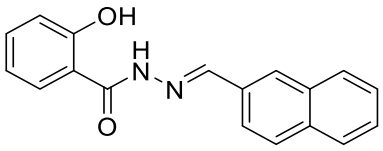
White powder; yield = 93%; m.p. 276 – 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 1H), 11.68 (s, 1H), 8.50 (s, 1H), 7.92 (s, 4H), 7.88 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.08-6.85 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 158.7, 146.5, 138.6, 134.0, 132.8, 128.9, 127.8, 119.1, 118.7, 117.3, 116.3, 112.1. HRMS calcd. for $C_{15}H_{11}N_3O_2$ $[M+H]^+$: 265.0851, found: 265.0868.

3.2.3.19 2-Hydroxy-*N*'-(4-nitrobenzylidene)benzohydrazide (51u)



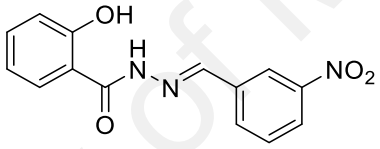
Pale yellow powder; yield = 94%; m.p. 276 – 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 11.66 (s, 1H), 8.55 (s, 1H), 8.31 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.10-6.86 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 158.6, 148.0, 146.0, 140.5, 134.0, 129.0, 128.2, 124.1, 119.2, 117.2, 116.4. HRMS calcd. for $C_{14}H_{11}N_3O_4$ $[M+H]^+$: 285.0750, found: 285.0772.

3.2.3.20 2-Hydroxy-*N*'-(naphthalen-2-ylmethylene)benzohydrazide (51v)



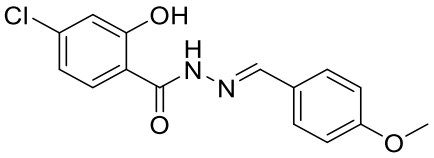
White powder; yield = 92%; m.p. 266 – 272 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 11.88 (s, 1H), 8.62 (s, 1H), 8.21 (s, 1H), 8.10-7.87 (m, 5H), 7.66-7.51 (m, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.06-6.93 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8, 159.0, 148.6, 133.9, 132.9, 131.9, 129.1, 128.6, 128.5, 128.4, 127.8, 127.3, 126.8, 122.7, 119.0, 117.3, 116.0. HRMS calcd. for $C_{18}H_{14}N_2O_2$ $[M+H]^+$: 290.1055, found: 290.1073.

3.2.3.21 2-Hydroxy-*N*'-(3-nitrobenzylidene)benzohydrazide (51w)



White powder; yield = 89%; m.p. 246 – 248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 11.70 (s, 1H), 8.57 (s, 1H), 8.52 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.08-6.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.7, 158.6, 148.2, 146.1, 136.0, 133.9, 133.5, 130.5, 129.0, 124.4, 121.1, 119.1, 117.2, 116.3. HRMS calcd. for $C_{14}H_{11}N_3O_4$ $[M+H]^+$: 285.0750, found: 285.0769.

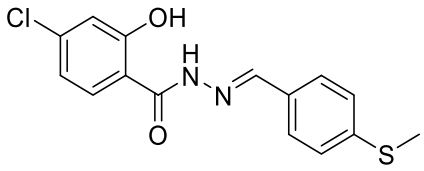
3.2.3.22 4-Chloro-2-hydroxy-*N*'-(4-methoxybenzylidene)benzohydrazide (51x)



Pale brown powder; yield = 76%; m.p. 266 – 270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.21 (s, 1H), 11.73 (s, 1H), 8.38 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.13-6.99 (m, 4H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6,

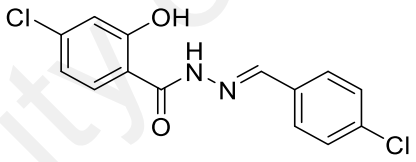
161.1, 159.6, 148.9, 137.5, 130.3, 129.0, 126.6, 119.2, 116.9, 115.5, 114.4, 55.3. HRMS calcd. for $C_{15}H_{13}ClN_2O_3$ $[M+H]^+$: 304.0615, found: 304.0626.

3.2.3.23 4-Chloro-2-hydroxy-*N*'-(4-(methylthio)benzylidene)benzohydrazide (51y)



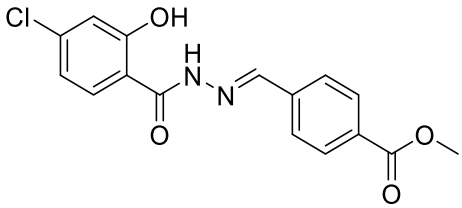
Pale brown crystal; yield = 62%; m.p. 255 – 258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s, 1H), 11.79 (s, 1H), 8.39 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.12-6.98 (m, 2H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 159.5, 148.5, 141.4, 137.6, 130.4, 127.7, 125.6, 119.2, 116.9, 115.7, 14.2. HRMS calcd. for $C_{15}H_{13}ClN_2O_2S$ $[M+H]^+$: 320.0386, found: 320.0397.

3.2.3.24 4-Chloro-*N*'-(4-chlorobenzylidene)-2-hydroxybenzohydrazide (51z)



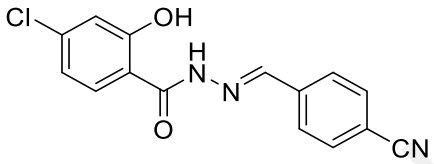
White powder; yield = 71%; m.p. 276 – 278 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 11.86 (s, 1H), 8.43 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.13-6.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 159.4, 148.5, 137.6, 134.8, 133.0, 130.5, 129.0, 128.9, 119.3, 116.8, 115.7. HRMS calcd. for $C_{14}H_{10}Cl_2N_2O_2$ $[M+H]^+$: 308.0119, found: 308.0131.

3.2.3.25 Methyl 4-((2-(4-chloro-2-hydroxybenzoyl)hydrazono)methyl)benzoate (51aa)



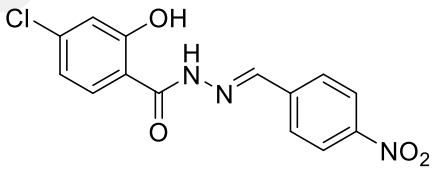
Pale brown powder; yield = 91%; m.p. 290 – 293 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.94 (s, 2H), 8.48 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 3H), 7.16-6.99 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.8, 163.7, 159.2, 147.3, 138.5, 137.6, 130.7, 129.7, 127.4, 119.3, 116.8, 116.0, 52.3. HRMS calcd. for $C_{16}H_{13}ClN_2O_4$ $[M+H]^+$: 332.0564, found: 332.0602.

3.2.3.26 4-Chloro-*N*'-(4-cyanobenzylidene)-2-hydroxybenzohydrazide (51ab)



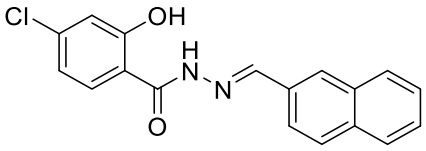
Pale brown powder; yield = 76%; m.p. 277 – 280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.97 (s, 2H), 8.48 (s, 1H), 7.91 (s, 4H), 7.86 (d, J = 8.6 Hz, 1H), 7.14-6.98 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 159.1, 146.7, 138.6, 137.7, 132.8, 130.8, 127.8, 119.4, 118.6, 116.8, 116.0, 112.1. HRMS calcd. for $C_{15}H_{10}ClN_3O_2$ $[M+H]^+$: 299.0462, found: 299.0474.

3.2.3.27 4-Chloro-2-hydroxy-*N*'-(4-nitrobenzylidene)benzohydrazide (51ac)



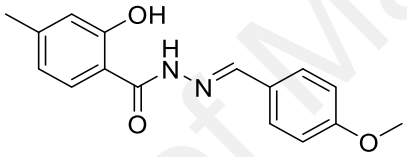
Pale yellow powder; yield = 88%; m.p. 276 – 281 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.01 (s, 2H), 8.53 (s, 1H), 8.30 (d, J = 9.1 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 1H), 7.12-7.00 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 159.0, 148.0, 146.2, 140.4, 137.7, 130.8, 128.2, 124.1, 119.4, 116.8, 116.1. HRMS calcd. for $C_{14}H_{10}ClN_3O_4$ $[M+H]^+$: 319.0360, found: 319.0371.

3.2.3.28 4-Chloro-2-hydroxy-*N*'-(naphthalen-2-ylmethylene)benzohydrazide (51ad)



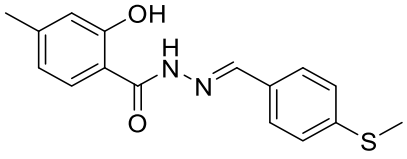
White powder; yield = 88%; m.p. 255 – 259 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (s, 1H), 11.92 (s, 1H), 8.60 (s, 1H), 8.18 (s, 1H), 8.05-7.86 (m, 5H), 7.62-7.49 (m, 2H), 7.14-7.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 159.5, 148.8, 137.6, 133.9, 132.9, 131.8, 130.5, 129.2, 128.6, 128.4, 127.8, 127.3, 126.9, 122.7, 119.3, 116.9, 115.8. HRMS calcd. for $C_{18}H_{13}ClN_2O_2$ $[M+H]^+$: 324.0666, found: 324.0676.

3.2.3.29 2-Hydroxy-*N*'-(4-methoxybenzylidene)-4-methylbenzohydrazide (51ae)



Brown crystal; yield = 50%; m.p. 216 – 220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.09 (s, 1H), 11.72 (s, 1H), 8.40 (s, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 7.8 Hz, 2H), 3.81 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 161.0, 159.8, 148.6, 144.5, 128.9, 128.0, 126.7, 119.9, 117.6, 114.4, 112.4, 55.3, 21.1. HRMS calcd. for $C_{16}H_{16}N_2O_3$ $[M+H]^+$: 284.1161, found: 284.1174.

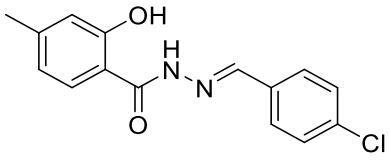
3.2.3.30 2-Hydroxy-4-methyl-*N*'-(4-(methylthio)benzylidene)benzohydrazide (51af)



Pale brown crystal; yield = 57%; m.p. 200 – 202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 11.78 (s, 1H), 8.41 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.81-6.75 (m, 2H), 2.52 (s, 3H), 2.30 (s, 3H). ^{13}C NMR

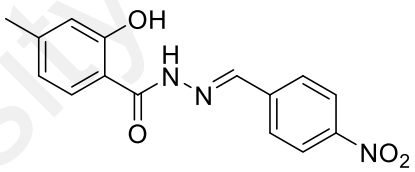
(100 MHz, DMSO-d_6): δ 165.0, 159.6, 148.3, 144.6, 141.3, 130.5, 128.2, 127.7, 125.6, 120.0, 117.6, 112.5, 21.2, 14.2. HRMS calcd. for $C_{16}H_{16}N_2O_2S$ $[M+H]^+$: 300.0932, found: 300.0944.

3.2.3.31 *N*'-(4-chlorobenzylidene)-2-hydroxy-4-methylbenzohydrazide (51ag)



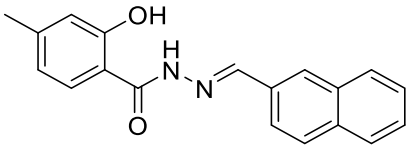
Brown crystal; yield = 57%; m.p. 208 – 211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.95 (s, 1H), 11.87 (s, 1H), 8.45 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 6.82-6.75 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.1, 159.5, 147.2, 144.7, 134.7, 133.1, 129.0, 128.8, 128.3, 120.0, 117.5, 112.6, 21.2. HRMS calcd. for $C_{15}H_{13}ClN_2O_2$ $[M+H]^+$: 288.0666, found: 288.0677.

3.2.3.32 2-Hydroxy-4-methyl-*N*'-(4-nitrobenzylidene)benzohydrazide (51ah)



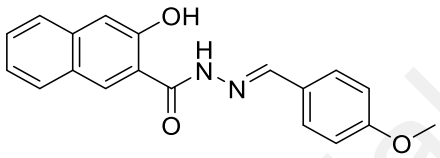
Pale brown powder; yield = 80%; m.p. 287 – 292 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 11.80 (s, 1H), 8.56 (s, 1H), 8.32 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 8.7 Hz, 2H), 7.81 (d, J = 8.2 Hz, 1H), 6.85-6.76 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 159.2, 147.9, 145.9, 144.8, 140.5, 128.6, 128.1, 124.1, 120.1, 117.5, 112.8, 21.2. HRMS calcd. for $C_{15}H_{13}N_3O_4$ $[M+H]^+$: 299.0906, found: 299.0920.

3.2.3.33 2-Hydroxy-4-methyl-*N*'-(naphthalen-2-ylmethylene)benzohydrazide (51ai)



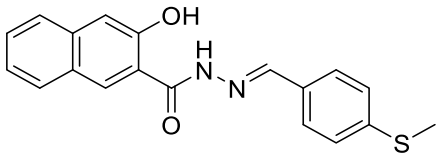
White crystal; yield = 84%; m.p. 240 – 243 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 11.92 (s, 1H), 8.60 (s, 1H), 8.17 (s, 1H), 8.11-7.91 (m, 4H), 7.85 (d, J = 7.7 Hz, 1H), 7.65-7.51 (m, 2H), 6.92-6.74 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.2, 159.7, 148.6, 144.8, 133.9, 132.9, 132.0, 129.1, 128.6, 128.5, 128.3, 127.9, 127.3, 126.9, 122.8, 120.1, 117.6, 112.6, 21.3. HRMS calcd. for $C_{19}H_{16}N_2O_2$ $[M+H]^+$: 304.1212, found: 304.1237.

3.2.3.34 3-Hydroxy-*N*'-(4-methoxybenzylidene)-2-naphthohydrazide (51aj)



Pale brown crystal; yield = 84%; m.p. 225 – 227 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.90 (s, 1H), 11.38 (s, 1H), 8.46 (s, 1H), 8.41 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.05 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 161.0, 154.2, 148.5, 135.8, 130.2, 128.9, 128.7, 128.2, 126.8, 126.7, 125.9, 123.8, 120.3, 114.4, 110.6, 55.4. HRMS calcd. for $C_{19}H_{16}N_2O_3$ $[M+H]^+$: 320.1161, found: 320.1181.

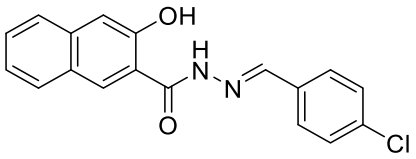
3.2.3.35 3-Hydroxy-*N*'-(4-(methylthio)benzylidene)-2-naphthohydrazide (51ak)



White crystal; yield = 85%; m.p. 239 – 242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.95 (s, 1H), 11.32 (s, 1H), 8.46 (s, 1H), 8.42 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.40-7.30 (m, 4H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 154.1, 148.1, 141.3, 135.8, 130.5,

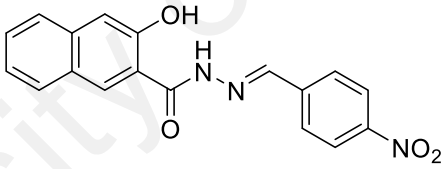
130.3, 128.7, 128.2, 127.7, 126.8, 125.9, 125.6, 123.8, 120.4, 110.6, 14.2. HRMS calcd. for $C_{19}H_{16}N_2O_2S$ $[M+H]^+$: 336.0932, found: 336.0960.

3.2.3.36 *N*'-(4-chlorobenzylidene)-3-hydroxy-2-naphthohydrazide (51al)



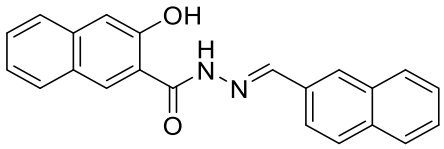
White crystal; yield = 89%; m.p. 260 – 264 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H), 11.27 (s, 1H), 8.46 (s, 1H), 8.45 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.82-7.71 (m, 3H), 7.60-7.47 (m, 3H), 7.40-7.32 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 153.9, 147.1, 135.9, 134.7, 133.1, 130.4, 129.0, 128.9, 128.7, 128.3, 126.8, 125.9, 123.8, 120.6, 110.6. HRMS calcd. for $C_{18}H_{13}ClN_2O_2$ $[M+H]^+$: 324.0666, found: 324.0690.

3.2.3.37 3-Hydroxy-*N*'-(4-nitrobenzylidene)-2-naphthohydrazide (51am)



Pale yellow powder; yield = 93%; m.p. 259 – 261 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.20 (s, 1H), 11.21 (s, 1H), 8.55 (s, 1H), 8.44 (s, 1H), 8.31 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.43-7.27 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 153.7, 148.0, 145.8, 140.5, 135.9, 130.7, 128.7, 128.3, 128.2, 126.9, 125.9, 124.1, 123.9, 120.8, 110.6. HRMS calcd. for $C_{18}H_{13}N_3O_4$ $[M+H]^+$: 335.0906, found: 335.0910.

3.2.3.38 3-Hydroxy-*N*'-(naphthalen-2-ylmethylene)-2-naphthohydrazide (51an)

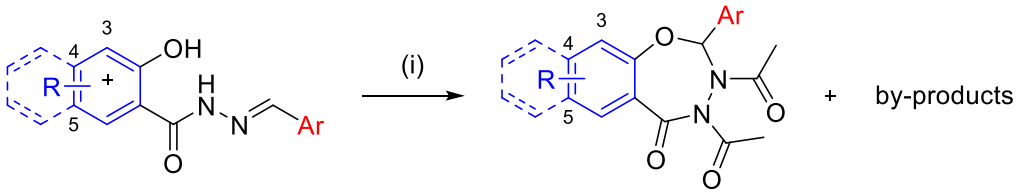


Pale yellow powder; yield = 90%; m.p. 254 – 258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (s, 1H), 11.33 (s, 1H), 8.63 (s, 1H), 8.49 (s, 1H), 8.19 (s, 1H), 8.14-7.92 (m, 5H), 7.78 (d, J = 8.2 Hz, 1H), 7.68-7.55 (m, 2H), 7.55-7.48 (m, 1H), 7.43-7.29 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 154.1, 148.5, 135.9, 133.9, 132.9, 132.0, 130.3, 129.1, 128.7, 128.6, 128.4, 128.3, 127.9, 127.3, 126.8, 125.9, 123.9, 122.8, 120.6, 110.6. HRMS calcd. for $C_{22}H_{16}N_2O_2$ $[M+H]^+$: 340.1212, found: 340.1239.

3.2.4 General Procedure for the Synthesis of *N*,*N*'-Diacetyl Benzo-1,3,4-oxadiazepines 52

Mixing protocol (as mentioned in Chapter 4.1) is the method for the preparation of the final concentration of 4.50% (*v/v*) of concentrated H_2SO_4/acetic anhydride from 10% (*v/v*). Firstly, 0.100 mL of H_2SO_4 was mixed with 0.900 mL of acetic anhydride in a vial to prepare 10% (*v/v*) of concentrated H_2SO_4/acetic anhydride. Then, the corresponding **51a-b** or **51e-an** (0.4 mmol) were dissolved in acetic anhydride (0.955 mL). Lastly, 0.045 mL of 10% (*v/v*) of concentrated H_2SO_4/acetic anhydride was added into the reaction.

The corresponding **51a-b** or **51e-an** (0.4 mmol) were dissolved in acetic anhydride (0.955 mL) and 10% (*v/v*) of concentrated H_2SO_4/acetic anhydride was added into the hydrazone solution to make a final concentration of 4.50% (*v/v*). The resulting mixture was stirred until it turned clear. Distilled water (10 mL) was added to the mixture and the reaction was left to stir for an hour. The mixture was then extracted thrice with chloroform. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was further purified by column chromatography on silica gel (ethyl acetate/hexane, 1:9 as eluent) to afford the desired compound.

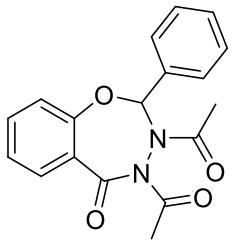


51a: R = H, Ar = *p*-MeS-C_6H_4, 85%
51b: R = H, Ar = *p*-Cl-C_6H_4, 87%
51e: R = H, Ar = C_6H_5, 73%
51f: R = 3-Me, Ar = C_6H_5, 98%
51g: R = 3-MeO, Ar = C_6H_5, 96%
51h: R = 3-Cl, Ar = C_6H_5, 40%
51i: R = 3-NO_2, Ar = C_6H_5, 62%
51j: R = 4-Me, Ar = C_6H_5, 80%
51k: R = 4-MeO, Ar = C_6H_5, 82%
51l: R = 4-Cl, Ar = C_6H_5, 90%
51m: R = 4-NO_2, Ar = C_6H_5, 70%
51n: R = 2-naphthyl, Ar = C_6H_5, 73%
51o: R = 5-Me, Ar = C_6H_5, 98%
51p: R = 5-MeO, Ar = C_6H_5, 86%
51q: R = 5-NO_2, Ar = C_6H_5, 64%
51r: R = H, Ar = *p*-MeO-C_6H_4, 90%
51s: R = H, Ar = *p*-MeO_2C-C_6H_4, 91%
51t: R = H, Ar = *p*-CN-C_6H_4, 93%
51u: R = H, Ar = *p*-NO_2-C_6H_4, 94%
51v: R = H, Ar = 2-naphthyl, 92%
51w: R = H, Ar = *m*-NO_2-C_6H_4, 89%
51x: R = 4-Cl, Ar = *p*-MeO-C_6H_4, 76%
51y: R = 4-Cl, Ar = *p*-MeS-C_6H_4, 62%
51z: R = 4-Cl, Ar = *p*-Cl-C_6H_4, 71%
51aa: R = 4-Cl, Ar = *p*-MeO_2C-C_6H_4, 91%
51ab: R = 4-Cl, Ar = *p*-CN-C_6H_4, 76%
51ac: R = 4-Cl, Ar = *p*-NO_2-C_6H_4, 88%
51ad: R = 4-Cl, Ar = 2-naphthyl, 88%
51ae: R = 4-Me, Ar = *p*-MeO-C_6H_4, 50%
51af: R = 4-Me, Ar = *p*-MeS-C_6H_4, 57%
51ag: R = 4-Me, Ar = *p*-Cl-C_6H_4, 57%
51ah: R = 4-Me, Ar = *p*-NO_2-C_6H_4, 80%
51ai: R = 4-Me, Ar = 2-naphthyl, 84%
51aj: R = 2-naphthyl, Ar = *p*-MeO-C_6H_4, 84%
51ak: R = 2-naphthyl, Ar = *p*-MeS-C_6H_4, 85%
51al: R = 2-naphthyl, Ar = *p*-Cl-C_6H_4, 89%
51am: R = 2-naphthyl, Ar = *p*-NO_2-C_6H_4, 93%
51an: R = 2-naphthyl, R' = 2-naphthyl, 90%

52a: R = H, Ar = *p*-MeS-C_6H_4, 79%
52b: R = H, Ar = *p*-Cl-C_6H_4, 36%
52e: R = H, Ar = C_6H_5, 54%
52f: R = 3-Me, Ar = C_6H_5, 39%
52g: R = 3-MeO, Ar = C_6H_5, 53%
52h: R = 3-Cl, Ar = C_6H_5, 34%
52i: R = 3-NO_2, Ar = C_6H_5, 14%
52j: R = 4-Me, Ar = C_6H_5, 46%
52k: R = 4-MeO, Ar = C_6H_5, 20%
52l: R = 4-Cl, Ar = C_6H_5, 60%
52m: R = 2-naphthyl, Ar = C_6H_5, 35%
52n: R = 5-Me, Ar = C_6H_5, 45%
52o: R = 5-MeO, Ar = C_6H_5, 48%
52p: R = 5-NO_2, Ar = C_6H_5, 46%
52q: R = H, Ar = *p*-MeO-C_6H_4, 69%
52r: R = H, Ar = *p*-MeO_2C-C_6H_4, 12%
52s: R = H, Ar = 2-naphthyl, 56%
52t: R = 4-Cl, Ar = *p*-MeO-C_6H_4, 83%
52u: R = 4-Cl, Ar = *p*-MeS-C_6H_4, 80%
52v: R = 4-Cl, Ar = *p*-Cl-C_6H_4, 51%
52w: R = 4-Cl, Ar = *p*-MeO_2C-C_6H_4, 15%
52x: R = 4-Cl, Ar = 2-naphthyl, 69%
52y: R = 4-Me, Ar = *p*-MeO-C_6H_4, 65%
52z: R = 4-Me, Ar = *p*-MeS-C_6H_4, 50%
52aa: R = 4-Me, Ar = *p*-Cl-C_6H_4, 24%
52ab: R = 4-Me, Ar = 2-naphthyl, 39%
52ac: R = 2-naphthyl, Ar = *p*-MeO-C_6H_4, 64%
52ad: R = 2-naphthyl, Ar = *p*-MeS-C_6H_4, 31%
52ae: R = 2-naphthyl, Ar = *p*-Cl-C_6H_4, 25%
52af: R = 2-naphthyl, Ar = 2-naphthyl, 34%

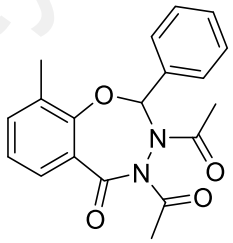
Scheme 3.4: Synthesis of *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepines **52** through intramolecular cyclization of *N*-(2-hydroxybenzoyl)hydrazones **51**. Reagents and conditions: (i) Ac_2O and 4.50% (*v*/*v*) of concentrated H_2SO_4, stir, r.t.

3.2.4.1 1,1'-(5-Oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52e)



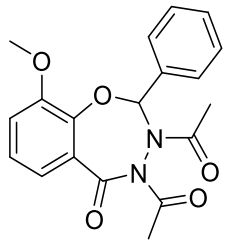
Off-white crystal; yield = 54%; m.p. 137 – 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.52 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49-7.42 (m, 2H), 7.33-7.26 (m, 4H), 7.23 (td, *J* = 7.7, 0.9 Hz, 1H), 7.14 (dd, *J* = 8.2, 0.9 Hz, 1H), 2.29 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.2, 169.1, 153.8, 135.9, 135.0, 131.0, 129.7, 128.6, 126.7, 126.4, 125.8, 122.7, 87.5, 25.1, 20.8. HRMS calcd. for $C_{18}H_{16}N_2O_4$ $[M+H]^+$: 324.1110, found: 324.1124.

3.2.4.2 1,1'-(9-Methyl-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52f)



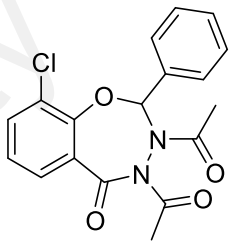
Pale yellow crystal; yield = 39%; m.p. 142 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55-7.49 (m, 2H), 7.45-7.40 (m, 1H), 7.37-7.30 (m, 3H), 7.23 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.5, 169.2, 151.6, 137.0, 135.1, 132.0, 129.6, 128.5, 128.4, 126.8, 126.7, 125.5, 86.7, 25.1, 20.8, 15.9. HRMS calcd. for $C_{19}H_{18}N_2O_4$ $[M+H]^+$: 338.1267, found: 338.1283.

3.2.4.3 1,1'-(9-Methoxy-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52g)



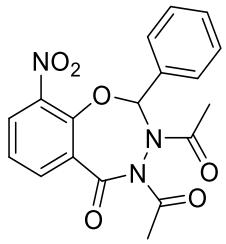
Pale yellow crystal; yield = 53%; m.p. 178 – 183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.33-7.28 (m, 4H), 7.27 (s, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 8.2, 1.4 Hz, 1H), 3.80 (s, 3H), 2.34 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.2, 169.1, 152.5, 142.6, 135.0, 129.6, 128.5, 128.0, 126.7, 126.2, 121.5, 117.8, 87.4, 56.5, 25.2, 20.8. HRMS calcd. for $C_{19}H_{18}N_2O_5$ $[M+H]^+$: 354.1216, found: 354.1234.

3.2.4.4 1,1'-(9-Chloro-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52h)



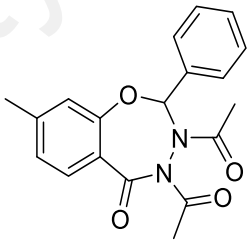
Pale yellow crystal; yield = 34%; m.p. 145 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.62 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.55-7.46 (m, 2H), 7.40-7.27 (m, 4H), 7.20 (t, *J* = 7.9 Hz, 1H), 2.35 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.3, 168.9, 149.4, 135.9, 134.4, 129.8, 129.1, 128.6, 128.5, 128.4, 126.7, 126.3, 87.5, 25.1, 20.7. HRMS calcd. for $C_{18}H_{15}ClN_2O_4$ $[M+H]^+$: 358.0720, found: 358.0734.

3.2.4.5 1,1'-(9-Nitro-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52i)



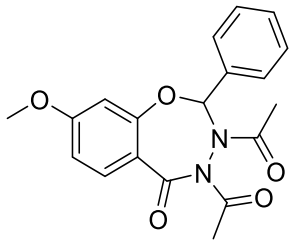
Pale yellow crystal; yield = 14%; m.p. 172 – 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.57 (s, 1H), 7.48-7.44 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.38-7.31 (m, 3H), 2.33 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 168.6, 168.4, 147.1, 144.2, 134.9, 133.8, 130.2, 130.0, 129.9, 128.7, 126.7, 125.9, 88.9, 25.2, 20.8. HRMS calcd. for $C_{18}H_{15}N_3O_6$ $[M+H]^+$: 369.0961, found: 369.0960.

3.2.4.6 1,1'-(8-Methyl-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52j)



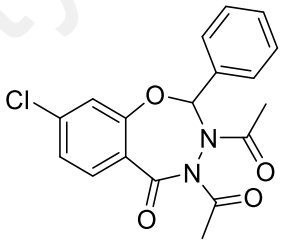
Pale yellow crystal; yield = 46%; m.p. 99 – 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.50-7.44 (m, 2H), 7.35-7.27 (m, 4H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.97 (s, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.1, 169.2, 153.8, 148.4, 135.1, 130.9, 129.6, 128.5, 126.7, 126.6, 123.2, 123.1, 87.3, 25.0, 21.8, 20.8. HRMS calcd. for $C_{19}H_{18}N_2O_4$ $[M+H]^+$: 338.1267, found: 338.1283.

3.2.4.7 1,1'-(8-Methoxy-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52k)



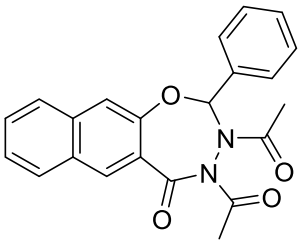
Pale yellow crystal; yield = 20%; m.p. 137 – 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.7 Hz, 1H), 7.49-7.43 (m, 2H), 7.37-7.28 (m, 4H), 6.77 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 2.27 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 169.7, 169.4, 166.0, 155.9, 135.0, 132.8, 129.7, 128.6, 126.7, 117.8, 112.3, 107.3, 87.2, 56.0, 24.9, 20.9. HRMS calcd. for $C_{19}H_{18}N_2O_5$ $[M+H]^+$: 354.1216, found: 354.1234.

3.2.4.8 1,1'-(8-Chloro-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52l)



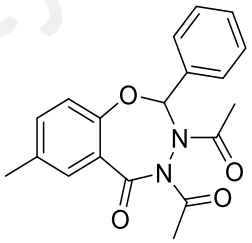
Pale brown crystal; yield = 60%; m.p. 87 – 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.53-7.40 (m, 2H), 7.35 (s, 1H), 7.34-7.26 (m, 3H), 7.24 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.17 (s, 1H), 2.29 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.2, 168.9, 154.3, 141.6, 134.5, 132.1, 129.8, 128.6, 126.7, 126.1, 124.5, 123.2, 87.5, 25.0, 20.7. HRMS calcd. for $C_{18}H_{15}ClN_2O_4$ $[M+H]^+$: 358.0720, found: 358.0720.

3.2.4.9 1,1'-(5-Oxo-2-phenylnaphtho[2,3-*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis (ethan-1-one) (52m)



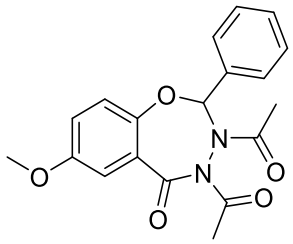
Pale brown crystal; yield = 35%; m.p. 200 – 203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.59 (s, 1H), 7.58-7.51 (m, 3H), 7.48 (td, *J* = 7.5, 0.9 Hz, 1H), 7.41-7.29 (m, 4H), 2.40 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.0, 169.2, 149.4, 137.0, 135.1, 132.9, 130.7, 129.7, 129.4, 129.3, 128.6, 127.7, 126.8, 126.7, 126.6, 119.8, 87.4, 25.2, 20.8. HRMS calcd. for $C_{22}H_{18}N_2O_4$ $[M+H]^+$: 374.1267, found: 374.1286.

3.2.4.10 1,1'-(7-Methyl-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52n)



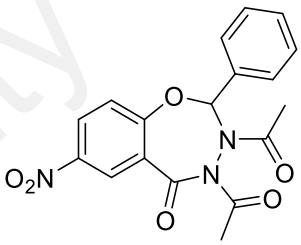
Pale yellow crystal; yield = 45%; m.p. 121 – 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 1.8 Hz, 1H), 7.51-7.41 (m, 2H), 7.41-7.29 (m, 4H), 7.26 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.3, 169.2, 151.6, 136.6, 135.7, 135.1, 131.0, 129.6, 128.5, 126.7, 126.0, 122.4, 87.4, 25.0, 20.9, 20.8. HRMS calcd. for $C_{19}H_{18}N_2O_4$ $[M+H]^+$: 338.1267, found: 338.1286.

3.2.4.11 1,1'-(7-Methoxy-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52o)



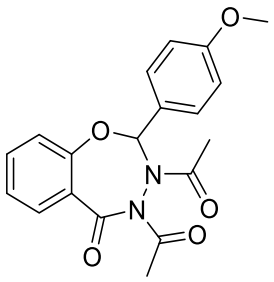
Pale yellow crystal; yield = 48%; m.p. 146 – 151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.46 (m, 2H), 7.36-7.29 (m, 3H), 7.26-7.21 (m, 2H), 7.11-7.07 (m, 2H), 3.79 (s, 3H), 2.33 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.1, 169.2, 157.2, 147.3, 135.2, 129.6, 128.5, 127.0, 126.6, 123.7, 121.8, 114.5, 87.6, 56.1, 25.0, 20.9. HRMS calcd. for $C_{19}H_{18}N_2O_5$ $[M+H]^+$: 354.1216, found: 354.1229.

3.2.4.12 1,1'-(7-Nitro-5-oxo-2-phenylbenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl) bis(ethan-1-one) (52p)



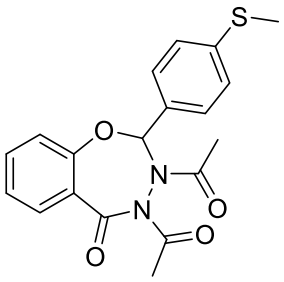
Pale brown crystal; yield = 46%; m.p. 178 – 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 2.7 Hz, 1H), 8.37 (dd, J = 9.1, 2.7 Hz, 1H), 7.49 (s, 1H), 7.42-7.26 (m, 6H), 2.25 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 168.6, 167.7, 158.2, 144.4, 133.5, 130.3, 130.1, 128.8, 127.7, 126.8, 125.5, 123.9, 87.6, 25.0, 20.6. HRMS calcd. for $C_{18}H_{15}N_3O_6$ $[M+H]^+$: 369.0961, found: 369.0963.

3.2.4.13 1,1'-(2-(4-Methoxyphenyl)-5-oxobenzo[f][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52q)



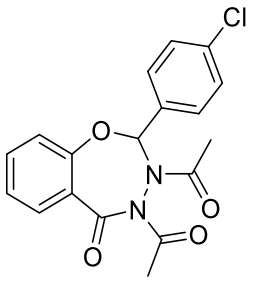
Off-white crystal; yield = 69%; m.p. 155 – 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.55 (td, *J* = 7.8, 1.7 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.32-7.21 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 2.34 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.2, 169.2, 160.5, 153.8, 135.8, 131.0, 128.0, 127.0, 126.4, 125.7, 122.7, 113.9, 87.4, 55.4, 25.1, 20.8. HRMS calcd. for $C_{19}H_{18}N_2O_5$ $[M+H]^+$: 354.1216, found: 354.1226.

3.2.4.14 1,1'-(2-(4-(Methylthio)phenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*, 5*H*)-diyl)bis(ethan-1-one) (52a)



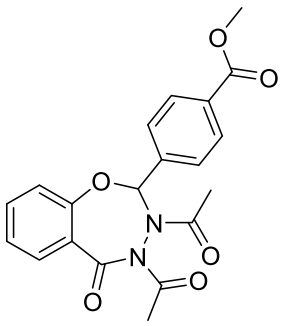
Off-white crystal; yield = 79%; m.p. 146 – 151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (td, *J* = 7.8, 1.7 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.29-7.24 (m, 2H), 7.18-7.13 (m, 3H), 2.41 (s, 3H), 2.34 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.1, 169.2, 153.7, 140.5, 135.9, 131.5, 131.0, 127.1, 126.4, 126.0, 125.8, 122.7, 87.3, 25.2, 20.8, 15.6. HRMS calcd. for $C_{19}H_{18}N_2O_4S$ $[M+H]^+$: 370.0987, found: 370.0999.

3.2.4.15 1,1'-(2-(4-Chlorophenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52b)



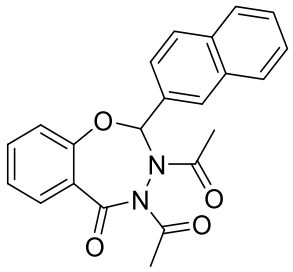
Off-white crystal; yield = 36%; m.p. 184 – 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.56 (td, *J* = 7.8, 1.5 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.32-7.26 (m, 3H), 7.25 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 2.36 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.0, 169.2, 153.5, 135.9, 133.5, 133.6, 131.0, 128.8, 128.1, 126.5, 126.1, 122.7, 86.9, 25.2, 20.8. HRMS calcd. for $C_{18}H_{15}ClN_2O_4$ $[M+H]^+$: 358.0720, found: 358.0728.

3.2.4.16 Methyl 4-(3,4-diacetyl-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,3,4]oxadiazepin-2-yl)benzoate (52r)



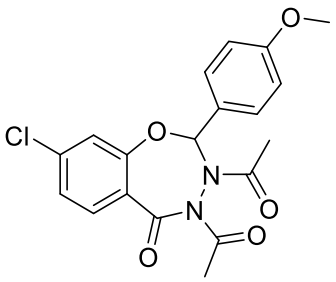
Off-white crystal; yield = 12%; m.p. 175 – 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.72-7.53 (m, 3H), 7.32 (s, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 3.85 (s, 3H), 2.33 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.0, 169.1, 166.7, 153.5, 139.8, 136.0, 131.2, 131.0, 129.8, 126.8, 126.5, 126.1, 122.7, 87.0, 52.4, 25.1, 20.8. HRMS calcd. for $C_{20}H_{18}N_2O_6$ $[M+H]^+$: 382.1165, found: 382.1174.

3.2.4.17 1,1'-(2-(Naphthalen-2-yl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52s)



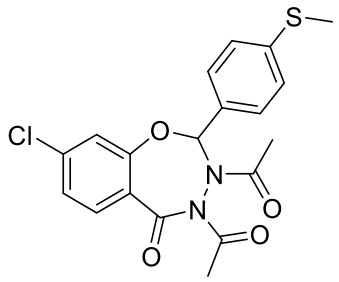
Off-white crystal; yield = 56%; m.p. 177 – 179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.85-7.73 (m, 4H), 7.57 (td, *J* = 7.7, 1.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.49-7.40 (m, 3H), 7.27 (td, *J* = 7.7, 0.9 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 2.23 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 170.1, 169.0, 153.8, 135.9, 133.8, 132.9, 132.4, 131.0, 128.5, 128.4, 128.0, 126.9, 126.6, 126.5, 126.0, 125.9, 124.3, 122.8, 87.6, 25.0, 20.8. HRMS calcd. for $C_{22}H_{18}N_2O_4$ $[M+H]^+$: 374.1267, found: 374.1286.

3.2.4.18 1,1'-(8-Chloro-2-(4-methoxyphenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52t)



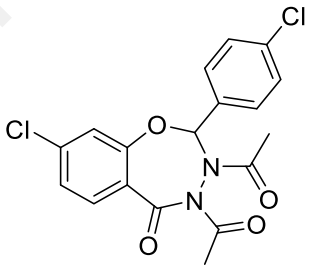
Off-white crystal; yield = 83%; m.p. 171 – 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.30 (s, 1H), 7.23 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.75 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 169.1, 168.9, 160.5, 154.3, 141.4, 132.0, 128.0, 126.4, 125.9, 124.5, 123.1, 133.9, 87.3, 55.4, 25.0, 20.7. HRMS calcd. for $C_{19}H_{17}ClN_2O_5$ $[M+H]^+$: 388.0826 , found: 388.0831.

3.2.4.19 1,1'-(8-Chloro-2-(4-(methylthio)phenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52u)



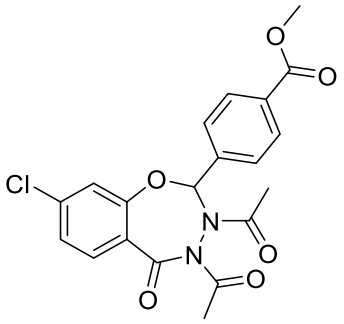
Off-white crystal; yield = 80%; m.p. 148 – 151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.7 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 7.24 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.19-7.13 (m, 3H), 2.42 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 169.1, 168.9, 154.2, 141.5, 140.7, 132.0, 130.8, 127.0, 126.0, 125.8, 124.5, 123.1, 87.2, 25.0, 20.7, 15.4. HRMS calcd. for $C_{19}H_{17}ClN_2O_4S$ $[M+H]^+$: 404.0598, found: 404.0599.

3.2.4.20 1,1'-(8-Chloro-2-(4-chlorophenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52v)



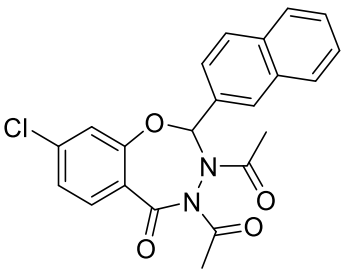
Off-white crystal; yield = 51%; m.p. 153 – 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.32-7.23 (m, 4H), 7.19 (d, *J* = 2.3 Hz, 1H), 2.34 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.1, 169.0, 154.1, 141.8, 135.7, 133.1, 132.0, 128.9, 128.1, 126.4, 124.7, 123.3, 87.0, 25.1, 20.8. HRMS calcd. for $C_{18}H_{14}Cl_2N_2O_4$ $[M+H]^+$: 392.0331, found: 392.0316.

3.2.4.21 Methyl 4-(3,4-diacetyl-8-chloro-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,3,4] oxadiazepin-2-yl)benzoate (52w)



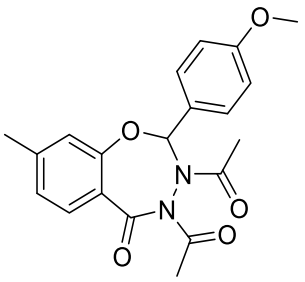
Off-white crystal; yield = 15%; m.p. 186 – 189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.36 (s, 1H), 7.28 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.20 (s, 1H), 3.86 (s, 3H), 2.30 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.1, 168.9, 166.7, 154.0, 141.8, 139.2, 132.1, 131.4, 129.8, 126.9, 126.5, 124.7, 123.3, 87.1, 52.5, 25.1, 20.7. HRMS calcd. for $C_{20}H_{17}ClN_2O_6$ $[M+H]^+$: 416.0775, found: 416.0768.

3.2.4.22 1,1'-(8-Chloro-2-(naphthalen-2-yl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4 (2*H*,5*H*)-diyl)bis(ethan-1-one) (52x)



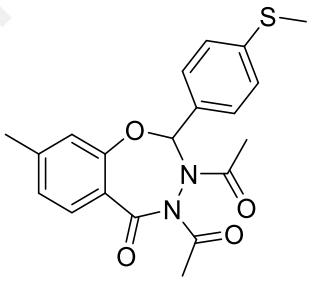
Off-white crystal; yield = 69%; m.p. 131 – 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.87-7.70 (m, 4H), 7.56-7.39 (m, 4H), 7.26 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 2.20 (s, 3H), 1.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.3, 168.9, 154.3, 141.7, 133.9, 132.9, 132.1, 131.9, 128.6, 128.4, 128.1, 127.1, 126.8, 126.2, 126.1, 124.7, 124.2, 123.3, 87.6, 25.0, 20.8. HRMS calcd. for $C_{22}H_{17}ClN_2O_4$ $[M+H]^+$: 408.0877, found: 408.0879.

3.2.4.23 1,1'-(2-(4-Methoxyphenyl)-8-methyl-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52y)



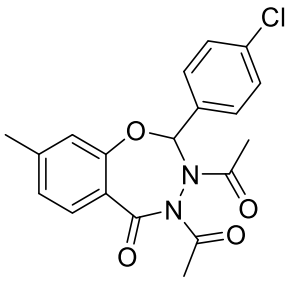
Pale brown crystal; yield = 65%; m.p. 138 – 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.25 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 6.82 (dd, *J* = 6.6, 2.1 Hz, 2H), 3.74 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.1, 169.2, 160.4, 153.8, 147.3, 130.9, 127.9, 127.1, 126.5, 123.2, 123.1, 113.8, 87.2, 55.3, 25.0, 21.8, 20.8. HRMS calcd. for $C_{20}H_{20}N_2O_5$ $[M+H]^+$: 368.1372, found: 368.1391.

3.2.4.24 1,1'-(8-Methyl-2-(4-(methylthio)phenyl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4(2*H*,5*H*)-diyl)bis(ethan-1-one) (52z)



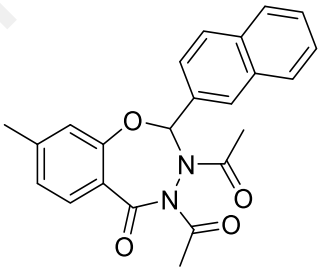
Pale yellow crystal; yield = 50%; m.p. 139 – 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.23 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.0, 169.2, 153.7, 147.4, 140.3, 131.5, 130.9, 127.1, 126.6, 125.9, 123.2, 123.1, 87.1, 25.1, 21.8, 20.8, 15.5. HRMS calcd. for $C_{20}H_{20}N_2O_4S$ $[M+H]^+$: 384.1144, found: 384.1154.

3.2.4.25 1,1'-(2-(4-Chlorophenyl)-8-methyl-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4 (2*H*,5*H*)-diyl)bis(ethan-1-one) (52aa)



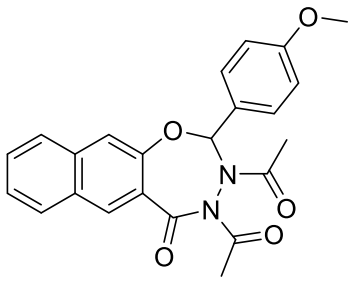
Pale brown crystal; yield = 24%; m.p. 142 – 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.24 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 170.0, 169.3, 153.6, 147.6, 135.5, 133.7, 131.0, 128.8, 128.1, 126.9, 123.4, 123.1, 86.8, 25.1, 21.9, 20.8. HRMS calcd. for $C_{19}H_{17}ClN_2O_4$ $[M+H]^+$: 372.0877, found: 372.0886.

3.2.4.26 1,1'-(8-Methyl-2-(naphthalen-2-yl)-5-oxobenzo[*f*][1,3,4]oxadiazepine-3,4 (2*H*,5*H*)-diyl)bis(ethan-1-one) (52ab)



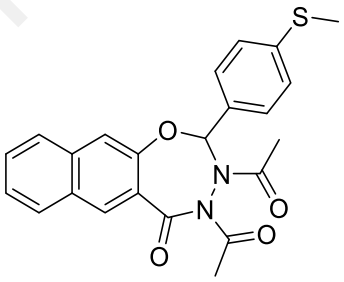
Off-white crystal; yield = 39%; m.p. 142 – 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.91-7.74 (m, 3H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.50 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.48-7.37 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.00 (s, 1H), 2.34 (s, 3H), 2.21 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 170.1, 169.2, 153.8, 147,5, 133.8, 132.9, 132.5, 130.9, 128.4, 128.0, 126.9, 126.7, 126.6, 126.0, 124.3, 123.4, 123.2, 87.4, 24.9, 21.9, 20.9. HRMS calcd. for $C_{23}H_{20}N_2O_4$ $[M+H]^+$: 388.1423, found: 388.1435.

3.2.4.27 1,1'-(2-(4-Methoxyphenyl)-5-oxonaphtho[2,3-*f*][1,3,4]oxadiazepine-3,4 (2*H*,5*H*)-diyl)bis(ethan-1-one) (52ac)



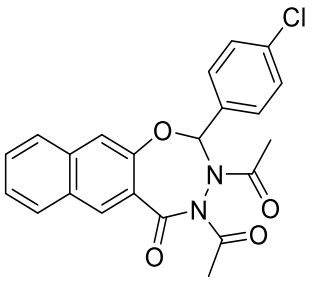
Off-white crystal; yield = 64%; m.p. 210 – 213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.56 (s, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.51-7.41 (m, 3H), 7.26 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.74 (s, 3H), 2.40 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.0, 169.3, 160.5, 149.4, 137.0, 132.8, 130.7, 129.4, 129.3, 127.9, 127.7, 127.2, 126.7, 126.6, 119.8, 113.9, 87.3, 55.4, 25.2, 20.9. HRMS calcd. for $C_{23}H_{20}N_2O_5$ $[M+H]^+$: 404.1372, found: 404.1384.

3.2.4.28 1,1'-(2-(4-(Methylthio)phenyl)-5-oxonaphtho[2,3-*f*][1,3,4]oxadiazepine-3,4 (2*H*,5*H*)-diyl)bis(ethan-1-one) (52ad)



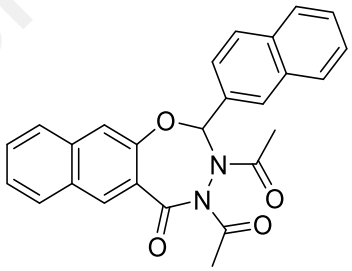
Off-white crystal; yield = 31%; m.p. 215 – 219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.61-7.53 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.26 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.0, 169.3, 149.4, 140.5, 137.0, 132.9, 131.6, 130.7, 129.4, 129.3, 127.7, 127.1, 126.8, 126.5, 126.0, 119.8, 87.2, 25.3, 20.9, 15.6. HRMS calcd. for $C_{23}H_{20}N_2O_4S$ $[M+H]^+$: 420.1144, found: 420.1155.

3.2.4.29 1,1'-(2-(4-Chlorophenyl)-5-oxonaphtho[2,3-*f*][1,3,4]oxadiazepine-3,4(2*H*, 5*H*)-diyl)bis(ethan-1-one) (52ae)



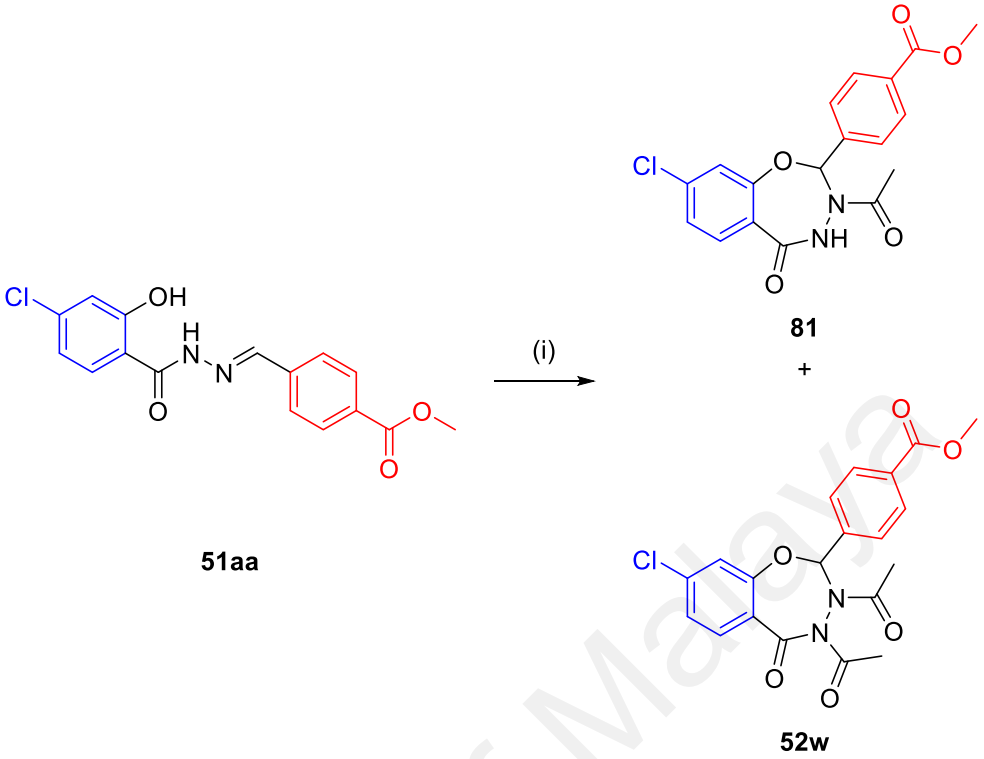
Off-white crystal; yield = 25%; m.p. 205 – 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.61-7.53 (m, 2H), 7.52-7.43 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.26 (s, 1H), 2.41 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.9, 169.3, 149.2, 137.0, 135.5, 133.7, 133.0, 130.8, 129.5, 129.3, 128.8, 128.1, 127.7, 126.9, 126.4, 119.8, 86.8, 25.3, 20.8. HRMS calcd. for $C_{22}H_{17}ClN_2O_4$ $[M+H]^+$: 408.0877, found: 408.0881.

3.2.4.30 1,1'-(2-(Naphthalen-2-yl)-5-oxonaphtho[2,3-*f*][1,3,4]oxadiazepine-3,4(2*H*, 5*H*)-diyl)bis(ethan-1-one) (52af)



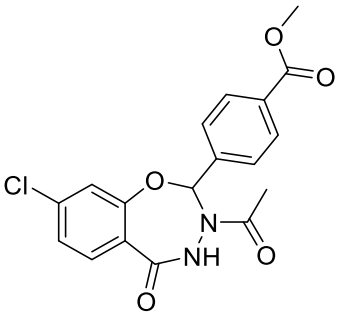
Off-white crystal; yield = 34%; m.p. 224 – 227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.07 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.84-7.76 (m, 4H), 7.65 (s, 1H), 7.60-7.54 (m, 2H), 7.52-7.42 (m, 4H), 2.31 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 170.0, 169.2, 149.4, 137.0, 133.9, 133.0, 132.9, 132.5, 130.8, 129.5, 129.3, 128.5, 128.1, 127.7, 126.9, 126.8, 126.6, 125.9, 124.3, 119.9, 87.5, 25.1, 20.9. HRMS calcd. for $C_{26}H_{20}N_2O_4$ $[M+H]^+$: 424.1423, found: 424.1434.

3.2.4.31 Isolation of 81 and 52w from Intramolecular Cyclization of 51aa



Scheme 3.5: Intramolecular cyclization of **51aa** to afford **81** and **52w**. Reagents and conditions: (i) Ac_2O and 4.50% (*v/v*) of concentrated H_2SO_4, stir, r.t.

3.2.4.32 Methyl 4-(3-acetyl-8-chloro-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,3,4] oxadiazepin-2-yl)benzoate (81)



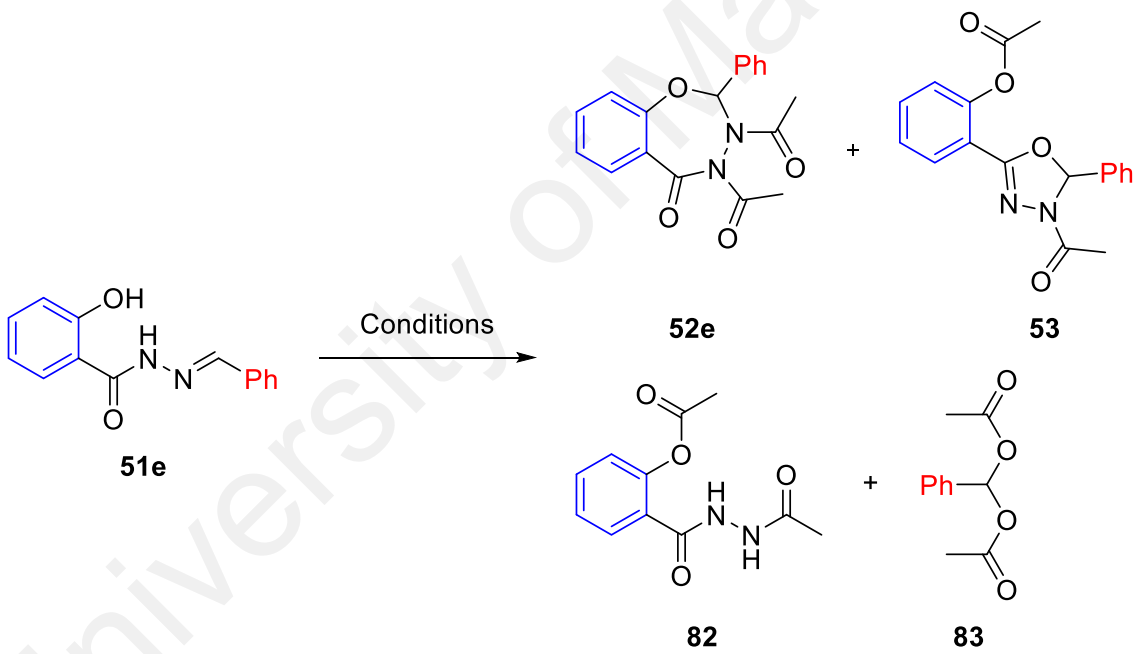
Pale brown solid; yield = 5%; m.p. 175 – 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.35 (s, 1H), 7.22 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 3.85 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 171.2, 166.7, 154.1, 140.5, 140.1, 131.4, 131.2, 130.2, 126.7, 126.2, 123.7, 123.1, 88.2, 52.6, 21.6. HRMS calcd. for $C_{18}H_{15}ClN_2O_5$ $[M+H]^+$: 374.0669, found: 374.0684.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Optimization of Reaction Condition

The reaction of *N*'-benzylidene-2-hydroxybenzohydrazide **51e** was chosen as a model reaction to examine the reaction conditions for the cyclization of **51** to form desired compound **52e**. The by-products formed in this reaction were identified as benzo-1,3,4-oxadiazole **53** and hydrolyzed compounds (**82** and **83**). Various Brønsted acids were used as catalyst to determine the best catalyst for the optimization of reaction condition. The results of these reactions are shown in Table 4.1.

Table 4.1. Optimization of the reaction conditions[a].



Entry	Acid	Additive[b]	Concentration of acid used, % (*v*/*v*)	Yield (%)[c]
1	Acetic acid	-	2.00	0
2	HCl	-	2.00	0
3	TFA	-	2.00	0
4	MsOH	-	2.00	traces
5	TsOH	-	2.00	23
6	TfOH	-	2.00	39

Table 4.1, continued. Optimization of the reaction conditions[a].

Entry	Acid	Additive[b]	Concentration of acid used, % (*v*/*v*)	Yield (%)[c]
7	H_2SO_4	-	2.00	43
8[d]	H_2SO_4	-	2.00	32
9	-	$KHSO_4$	2.00	42
10	HCl	$KHSO_4$	2.00	28
11	-	Na_2SO_4	2.00	0
12	HCl	Na_2SO_4	2.00	0
13	H_2SO_4	-	1.00	36
14	H_2SO_4	-	2.50	44
15	H_2SO_4	-	3.00	45
16	H_2SO_4	-	3.50	46
17	H_2SO_4	-	4.00	48
18	H_2SO_4	-	4.50	54
19	H_2SO_4	-	5.00	43
20	H_2SO_4	-	7.00	38
21	H_2SO_4	-	15.00	29

[a] Unless indicated otherwise, the reaction was carried out in 0.4 mmol of **51e** in acetic anhydride (V_t = 1 mL) at room temperature for about 5 minutes (refer to Chapter 3.2.4). [b] Additive added (0.8 mmol). [c] Isolated yield of **52e**. [d] Reaction was carried out at 0 °C.

In our hands, the use of acetic acid as a catalyst (Alhadi *et al.*, 2015) did not lead to the formation of **52e** (Table 4.1, entry 1). Thus, a series of Brønsted acids (Table 4.1, entries 2-7) was then screened as the possible catalytic substitutes. However, we did not obtain the desired product **52e** when either HCl (Table 4.1, entry 2) or TFA (Table 4.1, entry 3) were used as catalyst. The formation of **52e** was observed only when sulfur oxoacid was used (Table 4.1, entries 4-7). In addition, the catalytic activity of H_2SO_4 (Table 4.1, entry 7) outperformed the others, leading to the formation of **52e** with a 43%

yield. A lower yield (32%) was observed when the reaction was carried out at 0 °C (Table 4.1, entry 8).

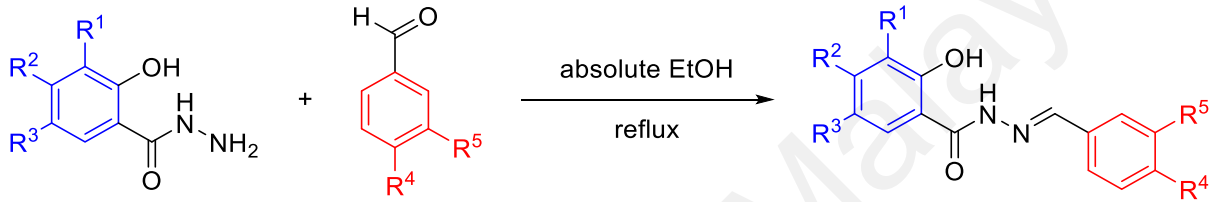
To validate the importance of sulfur oxoacid in the reaction, $KHSO_4$ or Na_2SO_4 was used as additive (Table 4.1, entries 9-12). Compound **52e** (42% yield) was observed to be formed when $KHSO_4$ was used (Table 4.1, entry 9). A lower yield (28%) was obtained when HCl and $KHSO_4$ were added to the **51e**/acetic anhydride solution (Table 4.1, entry 10) while addition of Na_2SO_4 under either acidic or normal (only acetic anhydride) conditions, failed to produce any seven-membered ring product **52e** (Table 4.1, entries 11 and 12). However, to date, the participation of sulfur oxoacid in the reaction is still unknown and further investigations may be conducted.

In the preliminary screening, it was observed that 43% yield of product **52e** was obtained with the use of 2.00% (*v/v*) of H_2SO_4 (Table 4.1, entry 7). Hence, the concentrations of H_2SO_4 were evaluated to further improve the yield of **52e** (Table 4.1, entries 13-21). The best yield of product **52e** from intramolecular cyclization of **51e** was 54% when 4.50% (*v/v*) of H_2SO_4 was used (Table 4.1, entry 18). Besides the optimization of the H_2SO_4 concentration, the mixing protocol was found to be crucial in order to maximize the formation of desired product **52e** (refer to Chapter 3.2.4 for more details). This mixing protocol is imperative to obtain a good yield of the product. A slight change in the protocol will result in lower yield of the product (data not shown). Thus, we used these set conditions as the optimized conditions and used in the subsequent study of the cyclization of various **51**.

4.2 Synthesis of *N*-(2-Hydroxybenzoyl)hydrazones 51

Compound **51**, as intermediate in the synthesis of **52**, was easily synthesized through the condensation between **65** and **69**. The synthesized compounds were obtained in moderate to good yields and are summarized in Table 4.2.

Table 4.2. Summary of synthesized *N*-(2-hydroxybenzoyl)hydrazones **51**.



65a-m **69a-i** **51a-b, e-an**

Entry	R^1	R^2	R^3	R^4	R^5	**51**					
						Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
								Reported	Found	Calculated	Found
1	H	H	H	H	H	**51e**	73	237 – 239	242 – 246	240.0899	240.0920
2	Me	H	H	H	H	**51f**	98	-	167 – 169	254.1055	254.1078
3	MeO	H	H	H	H	**51g**	96	-	103 – 107	270.1004	270.1007
4	Cl	H	H	H	H	**51h**	40	-	161 – 165	274.0509	274.0529
5[b]	NO_2	H	H	H	H	**51i**	62	-	203 – 208	285.0750	285.0764
6	H	Me	H	H	H	**51j**	80	-	226 – 229	254.1055	254.1063
7	H	MeO	H	H	H	**51k**	82	-	205 – 209	270.1004	270.1012

Table 4.2, continued. Summary of synthesized *N*-(2-hydroxybenzoyl)hydrazones **51**.

Entry	R^1	R^2	R^3	R^4	R^5	**51**					
						Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
								Reported	Found	Calculated	Found
8	H	Cl	H	H	H	**51l**	90	243	261 – 264	274.0509	274.0527
9[b]	H	NO_2	H	H	H	**51m**	70	-	340 (decomp)	285.0750	285.0763
10	H	naphthyl		H	H	**51n**	73	224 – 225	227 – 230	290.1055	290.1076
11	H	H	Me	H	H	**51o**	98	-	207 – 209	254.1055	254.1079
12	H	H	MeO	H	H	**51p**	86	-	223 – 228	270.1004	270.1028
13[b]	H	H	NO_2	H	H	**51q**	64	216 – 218	252 – 255	285.0750	285.0763
14	H	H	H	MeO	H	**51r**	90	215 – 217	224 – 226	270.1004	270.1028
15	H	H	H	MeS	H	**51a**	85	-	245 – 250	286.0776	286.0781
16	H	H	H	Cl	H	**51b**	87	255 – 258	262 – 266	274.0509	274.0510
17	H	H	H	MeO_2C	H	**51s**	91	-	262 – 264	298.0954	298.0958
18	H	H	H	CN	H	**51t**	93	-	276 – 280	265.0851	265.0868

Table 4.2, continued. Summary of synthesized *N*-(2-hydroxybenzoyl)hydrazones **51**.

Entry	R^1	R^2	R^3	R^4	R^5	**51**					
						Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
								Reported	Found	Calculated	Found
19	H	H	H	NO_2	H	**51u**	94	278 – 280	276 – 280	285.0750	285.0772
20	H	H	H	naphthyl		**51v**	92	-	266 – 272	290.1055	290.1073
21	H	H	H	H	NO_2	**51w**	89	-	246 – 248	285.0750	285.0769
22	H	Cl	H	MeO	H	**51x**	76	246	266 – 270	304.0615	304.0626
23	H	Cl	H	MeS	H	**51y**	62	-	255 – 258	320.0386	320.0397
24	H	Cl	H	Cl	H	**51z**	71	-	276 – 278	308.0119	308.0131
25	H	Cl	H	MeO_2C	H	**51aa**	91	-	290 – 293	332.0564	332.0602
26	H	Cl	H	CN	H	**51ab**	76	-	277 – 280	299.0462	299.0474
27	H	Cl	H	NO_2	H	**51ac**	88	-	276 – 281	319.0360	319.0371
28	H	Cl	H	naphthyl		**51ad**	88	-	255 – 259	324.0666	324.0676
29	H	Me	H	MeO	H	**51ae**	50	-	216 – 220	284.1161	284.1174

Table 4.2, continued. Summary of synthesized *N*-(2-hydroxybenzoyl)hydrazones **51**.

Entry	R^1	R^2	R^3	R^4	R^5	**51**					
						Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
								Reported	Found	Calculated	Found
30	H	Me	H	SMe	H	**51af**	57	-	200 – 202	300.0932	300.0944
31	H	Me	H	Cl	H	**51ag**	57	-	208 – 211	288.0666	288.0677
32	H	Me	H	NO_2	H	**51ah**	80	-	287 – 292	299.0906	299.0920
33	H	Me	H	naphthyl		**51ai**	84	-	240 – 243	304.1212	304.1237
34	H	naphthyl		MeO	H	**51aj**	84	-	225 – 227	320.1161	320.1181
35	H	naphthyl		MeS	H	**51ak**	85	-	239 – 242	336.0932	336.0960
36	H	naphthyl		Cl	H	**51al**	89	-	260 – 264	324.0666	324.0690
37	H	naphthyl		NO_2	H	**51am**	93	-	259 – 261	335.0906	335.0910
38	H	naphthyl		naphthyl		**51an**	90	-	254 – 258	340.1212	340.1239

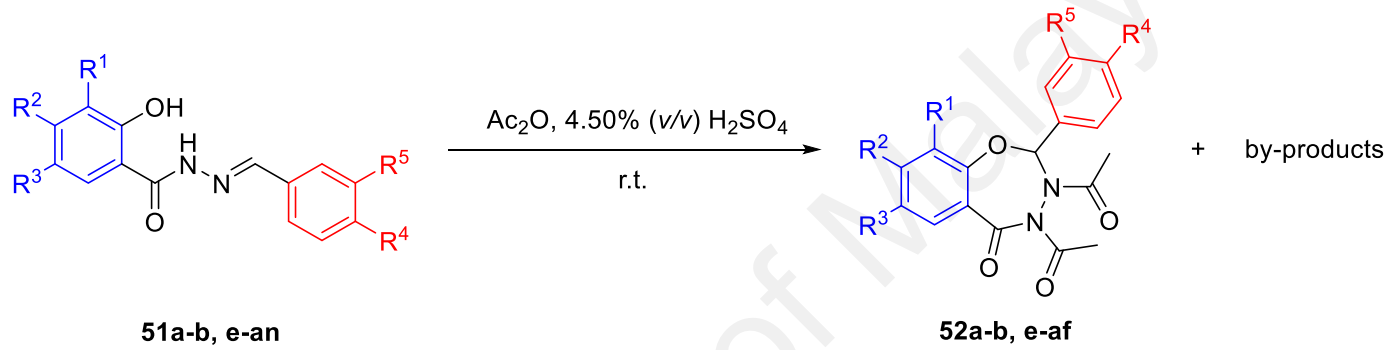
[a] Isolated yield. All products were identified by ^1H and ^{13}C NMR. [b] *L*-(+)-tartaric acid (45 mol %) was used as catalyst.

The nitro group is electron-withdrawing via inductive and resonance effects. The large inductive effect of NO_2 is the result of the formal + charge located on nitrogen. This electron deficiency withdraws electron density from the salicylic ring and causes a significant decrease in the nucleophilicity of hydrazides. Thus, only **51i**, **51m** and **51q** with NO_2 substituent on the hydrazides required *L*-(+)-tartaric acid as catalyst (Sim *et al.*, 2018) to optimize the reversibility of hydrazone formation (Kölmel & Kool, 2017).

4.3 Synthesis of *N*,*N*'-Diacetyl Benzo-1,3,4-oxadiazepines 52

Having identified the optimized reaction conditions, we then investigated the influences of different substituents on salicylic ring (R) and benzylidene ring (Ar) of **51** in the intramolecular cyclization reactions and the results of this study are displayed in Table 4.3.

Table 4.3. Summary of synthesized *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepines **52**.



51a-b, e-an **52a-b, e-af**

Entry	**51**	R^1	R^2	R^3	R^4	R^5	**52**					
							Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
									Reported	Found	Calculated	Found
1	**51e**	H	H	H	H	H	**52e**	54	-	137 – 140	324.1110	324.1124
2	**51f**	Me	H	H	H	H	**52f**	39	-	142 – 147	338.1267	338.1283
3	**51g**	MeO	H	H	H	H	**52g**	53	-	178 – 183	354.1216	354.1234
4	**51h**	Cl	H	H	H	H	**52h**	34	-	145 – 150	358.0720	358.0734
5	**51i**	NO_2	H	H	H	H	**52i**	14	-	172 – 176	369.0961	369.0960
6	**51j**	H	Me	H	H	H	**52j**	46	-	99 – 104	338.1267	338.1283

Table 4.3, continued. Summary of synthesized *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepines **52**.

Entry	**51**	R^1	R^2	R^3	R^4	R^5	**52**					
							Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
									Reported	Found	Calculated	Found
7	**51k**	H	MeO	H	H	H	**52k**	20	-	137 – 142	354.1216	354.1234
8	**51l**	H	Cl	H	H	H	**52l**	60	-	87 – 92	358.0720	358.0720
9	**51m**	H	NO_2	H	H	H	-	-	-	-	-	-
10	**51n**	H	naphthyl		H	H	**52m**	35	-	200 – 203	374.1267	374.1286
11	**51o**	H	H	Me	H	H	**52n**	45	-	121 – 126	338.1267	338.1286
12	**51p**	H	H	MeO	H	H	**52o**	48	-	146 – 151	354.1216	354.1229
13	**51q**	H	H	NO_2	H	H	**52p**	46	-	178 – 180	369.0961	369.0963
14	**51r**	H	H	H	MeO	H	**52q**	69	-	155 – 158	354.1216	354.1226
15	**51b**	H	H	H	MeS	H	**52a**	79	138	146 – 151	370.0987	370.0999
16	**51a**	H	H	H	Cl	H	**52b**	36	120	184 – 188	358.0720	358.0728
17	**51s**	H	H	H	MeO_2C	H	**52r**	12		175 – 178	382.1165	382.1174
18	**51t**	H	H	H	CN	H	-	-	-	-	-	-

Table 4.3, continued. Summary of synthesized *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepines **52**.

Entry	**51**	R^1	R^2	R^3	R^4	R^5	**52**					
							Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
									Reported	Found	Calculated	Found
19	**51u**	H	H	H	NO_2	H	-	-	-	-	-	-
20	**51v**	H	H	H	naphthyl		**52s**	56		177 – 179	374.1267	374.1286
21	**51w**	H	H	H	H	NO_2	-	-	-	-	-	-
22	**51x**	H	Cl	H	MeO	H	**52t**	83	-	171 – 174	388.0826	388.0831
23	**51y**	H	Cl	H	MeS	H	**52u**	80	-	148 – 151	404.0598	404.0599
24	**51z**	H	Cl	H	Cl	H	**52v**	51	-	153 – 157	392.0331	392.0316
25	**51aa**	H	Cl	H	MeO_2C	H	**52w**	15	-	186 – 189	416.0775	416.0768
26	**51ab**	H	Cl	H	CN	H	-	-	-	-	-	-
27	**51ac**	H	Cl	H	NO_2	H	-	-	-	-	-	-
28	**51ad**	H	Cl	H	naphthyl		**52x**	69	-	131 – 135	408.0877	408.0879
29	**51ae**	H	Me	H	MeO	H	**52y**	65	-	138 – 142	368.1372	368.1391
30	**51af**	H	Me	H	MeS	H	**52z**	50	-	139 – 143	384.1144	384.1154

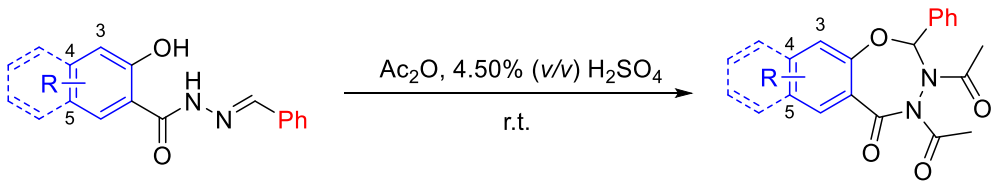
Table 4.3, continued. Summary of synthesized *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepines **52**.

Entry	**51**	R^1	R^2	R^3	R^4	R^5	**52**					
							Codes	Yield (%)[a]	m.p. (°C)		m.w. (g mol^{-1})	
									Reported	Found	Calculated	Found
31	**51ag**	H	Me	H	Cl	H	**52aa**	24	-	142 – 146	372.0877	372.0886
32	**51ah**	H	Me	H	NO_2	H	-	-	-	-	-	-
33	**51ai**	H	Me	H	naphthyl		**52ab**	39	-	142 – 145	388.1423	388.1435
34	**51aj**	H	naphthyl		MeO	H	**52ac**	64	-	210 – 213	404.1372	404.1384
35	**51ak**	H	naphthyl		MeS	H	**52ad**	31	-	215 – 219	420.1144	420.1155
36	**51al**	H	naphthyl		Cl	H	**52ae**	25	-	205 – 208	408.0877	408.0881
37	**51am**	H	naphthyl		NO_2	H	-	-	-	-	-	-
38	**51an**	H	naphthyl		naphthyl		**52af**	34	-	224 – 227	424.1423	424.1434

[a] Isolated yield. All products were identified by ^1H and ^{13}C NMR.

4.3.1 Synthesis of 52 with Substitution on the Salicylic Ring (R)

The study for the synthesis of **52** with substitution on the salicylic ring (R) was carried out and the results are displayed in Table 4.4.



51e-q **52e-p**

Table 4.4. Substrate scope of **51** with substituent on salicylic ring (R)[a].

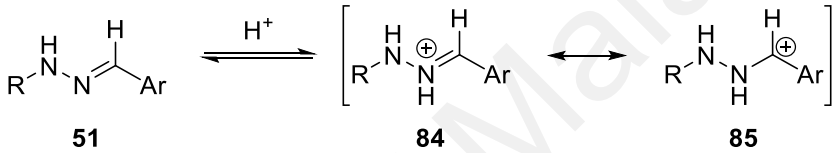
Entry	R (**51**)	**52**	Yield (%)[b]
1	H (**51e**)	**52e**	54
2	3-Me (**51f**)	**52f**	39
3	3-MeO (**51g**)	**52g**	53
4	3-Cl (**51h**)	**52h**	34
5	3-NO_2 (**51i**)	**52i**	14
6	4-Me (**51j**)	**52j**	46
7	4-MeO (**51k**)	**52k**	20
8	4-Cl (**51l**)	**52l**	60
9	4-NO_2 (**51m**)	-	-
10	2-naphthyl (**51n**)	**52m**	35
11	5-Me (**51o**)	**52n**	45
12	5-MeO (**51p**)	**52o**	48
13	5-NO_2 (**51q**)	**52p**	46

[a] Unless indicated otherwise, the reaction was carried out in 0.4 mmol scale catalyzed by 4.50% (*v/v*) of sulfuric acid in acetic anhydride (V_t = 1 mL) at room temperature for about 5 minutes. [b] Isolated yield of **52**.

The cyclization proceeded with most of electron-donating and withdrawing substituents (Table 4.4). Evidently, the substrate bearing a 4–Cl atom on the salicylic ring (R) in **51l** could efficiently be transformed into the corresponding product **52l** in 60%

yield (Table 4.4, entry 8). However, intramolecular cyclization of substrate bearing 4–NO_2 group in **51m** failed to yield its corresponding seven-membered ring product (Table 4.4, entry 9). Since the data showed that the substituent (H, Me, Cl and naphthyl) at 4-position of the salicylic ring (R) seem to greatly affect the chemical yield, we decided to study the corresponding substituent effect.

As postulated by Kölmel and Kool (2017), the formation of two resonance forms, i.e. **84** or **85** are due to the protonation of **51** (Scheme 4.1). The seven-membered ring product formed is presumably, due to the stability of the resonance form **85**.



Scheme 4.1. The formation of two resonance (**84** or **85**) forms from the protonation of **51**.

The formation of seven-membered ring products requires nucleophilic attack of intramolecular hydroxyl group on the electrophilic carbocation species **85**. Through resonance effect, the presence of electron-donating groups on either 3- or 5-position of the salicylic ring seems to enhance the stability of **85a** and **85b** (Figure 4.1a), leading to the higher yields of seven-membered ring products. However, the presence of electron-donating groups on 4-position would reduce the stability of **85c** (Figure 4.1b), providing lower yields of seven-membered ring products.

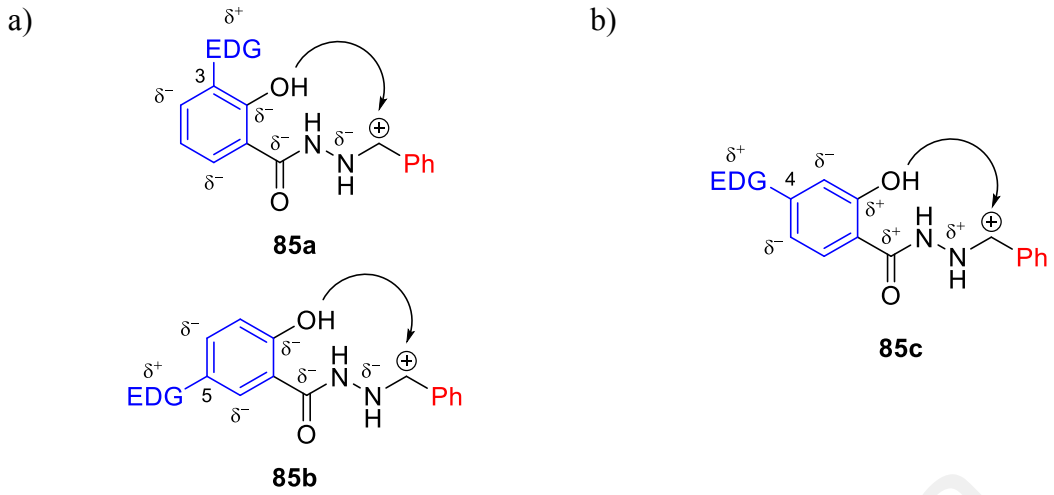


Figure 4.1. Resonance form with a) EDG on 3- (**85a**) or 5-position (**85b**); and b) EDG on 4-position (**85c**) of the salicylic ring with indication of the partial charges.

The presence of electron-withdrawing groups on either 3- or 5-position of the salicylic ring seems to reduce the stability of **85d** and **85e** (Figure 4.2a), giving lower yields of seven-membered ring products. On the other hand, the presence of electron-withdrawing groups on 4-position would enhance the stability of **85f** (Figure 4.2b), leading to the higher yields of seven-membered ring products.

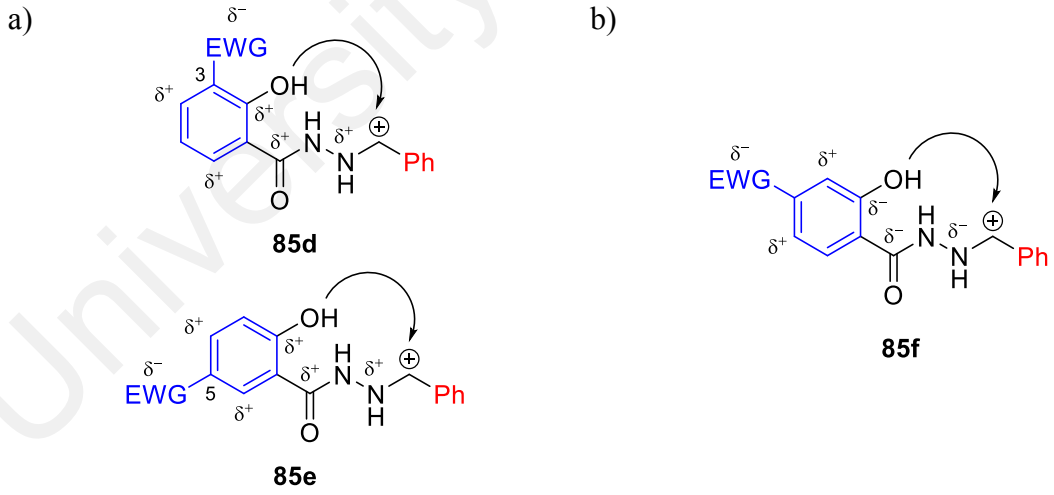
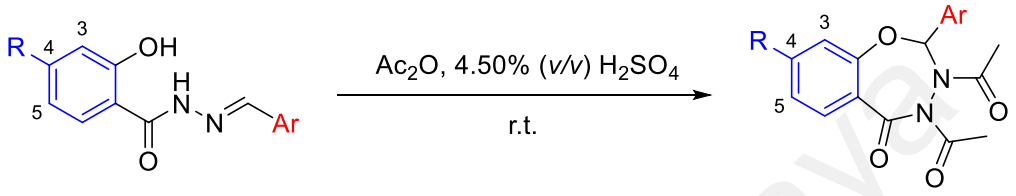


Figure 4.2. Resonance form with a) EWG on 3- (**85d**) or 5-position (**85e**); and b) EWG on 4-position (**85f**) of the salicylic ring with indication of the partial charges.

Through our observation, we noticed that Me and NO_2 substituents on salicylic ring did not follow the previous explanation. It is possible that there is an additional inductive effect which influences the nucleophilicity of hydroxyl group. However, it is only a hypothesis and further calculations need to be carried out to prove this hypothesis.

4.3.2 Synthesis of 52 with Substitution on Both Salicylic Ring (R) and Benzylidene Ring (Ar)

In the light of these encouraging results above, we further expanded the substrate scope of this intramolecular cyclization reaction using different substituents on both salicylic (R) and benzylidene (Ar) rings of **51** (Table 4.5).



51a-b, r-an **52a-b, q-af**

Table 4.5. Substrate scope of **51** with substitution on both salicylic (R) and benzylidene ring (Ar)[a].

Entry	R/Ar (**51**)	**52**	Yield (%)[b]
1	H/*p*-MeO-C_6H_4 (**51r**)	**52q**	69
2	H/*p*-MeS-C_6H_4 (**51a**)	**52a**	79
3	H/*p*-Cl-C_6H_4 (**51b**)	**52b**	36
4	H/*p*-MeO_2C-C_6H_4 (**51s**)	**52r**	12
5	H/*p*-CN-C_6H_4 (**51t**)	-	-
6	H/*p*-NO_2-C_6H_4 (**51u**)	-	-
7	H/2-naphthyl (**51v**)	**52s**	56
8	H/*m*-NO_2-C_6H_4 (**51w**)	-	-
9	4-Cl/*p*-MeO-C_6H_4 (**51x**)	**52t**	83
10	4-Cl/*p*-MeS-C_6H_4 (**51y**)	**52u**	80
11	4-Cl/*p*-Cl-C_6H_4 (**51z**)	**52v**	51
12	4-Cl/*p*-MeO_2C-C_6H_4 (**51aa**)	**52w**	15
13	4-Cl/*p*-CN-C_6H_4 (**51ab**)	-	-
14	4-Cl/*p*-NO_2-C_6H_4 (**51ac**)	-	-
15	4-Cl/2-naphthyl (**51ad**)	**52x**	69

Table 4.5, continued. Substrate scope of **51** with substitution on both salicylic (R) and benzylidene ring (Ar)[a].

Entry	R/Ar (**51**)	**52**	Yield (%)[b]
16	4-Me/*p*-MeO-C_6H_4 (**51ae**)	**52y**	65
17	4-Me/*p*-MeS-C_6H_4 (**51af**)	**52z**	50
18	4-Me/*p*-Cl-C_6H_4 (**51ag**)	**52aa**	24
19	4-Me/*p*-NO_2-C_6H_4 (**51ah**)	-	-
20	4-Me/2-naphthyl (**51ai**)	**52ab**	39
21	2-naphthyl/*p*-MeO-C_6H_4 (**51aj**)	**52ac**	64
22	2-naphthyl/*p*-MeS-C_6H_4 (**51ak**)	**52ad**	31
23	2-naphthyl/*p*-Cl-C_6H_4 (**51al**)	**52ae**	25
24	2-naphthyl/*p*-NO_2-C_6H_4 (**51am**)	-	-
25	2-naphthyl/2-naphthyl (**51an**)	**52af**	34

[a] Unless indicated otherwise, the reaction was carried out in 0.4 mmol scale catalyzed by 4.50% (*v/v*) of sulfuric acid in acetic anhydride (V_t = 1 mL) at room temperature for about 5 minutes. [b] Isolated yield of **52**.

With a given benzylidene group, the best cyclization was observed when R was Cl followed by when R was H. The substrates with methyl substituent as R and naphthyl ring instead of phenyl provided relatively lower chemical yields (Table 4.5).

As for the substituents on the benzylidene ring (Ar), electron-donating groups (OMe and SMe) at the *para* position gave higher yields than electron-withdrawing-groups (Cl, COOMe, CN and NO_2). The presence of strong electron-withdrawing groups such as CN and NO_2 (**51t**, **51u**, **51w**, **51ab**, **51ac**, **51ah** and **51am**) at either *meta* or *para* position of the benzylidene ring (Ar) of **51** did not give any seven-membered ring product. We were able to isolate the seven-membered ring products with weaker electron-withdrawing substituents such as Cl and COOMe at the *para* position on the benzylidene ring (Ar) (**52b**, **52r**, **52v**, **52w**, **52aa** and **52ae**). In addition, the formation of seven-membered ring

product (**52af**) is still viable with the substrate (**51an**) comprising two naphthyl rings, albeit low yield (Table 4.5, entry 38).

The presence of electron-donating groups on the benzylidene ring seems to enhance the stability of **85g** inductively (Figure 4.3a). Nucleophilic attack by hydroxyl group on the more stable carbocation species would lead to the higher yields of seven-membered ring products. On the other hand, intermediate **85h** is unstable due to the repulsion between the positive charged on the carbocation species and partial positive charges next to it during the presence of electron-withdrawing groups on the benzylidene ring (Figure 4.3b). Higher activation energy is required to form **85h**, leading to the formation of seven-membered ring products. Since the reactions were carried out in room temperature, no seven-membered ring product is observed.

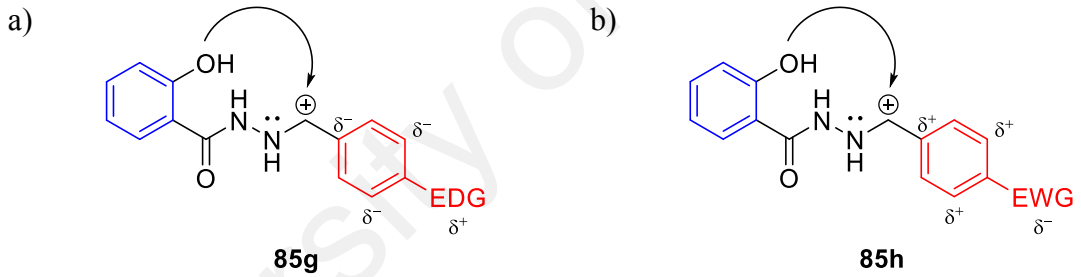


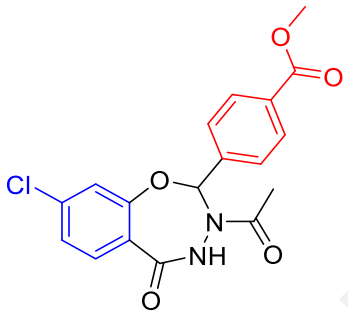
Figure 4.3. Resonance form with a) EDG (**85g**); and b) EWG (**85h**) on the benzylidene ring with indication of the partial charges.

Halogen substituents are both inductively electron-withdrawing (due to their electronegativity) and electron-donating through resonance (lone pair donation). Resonance effect is usually stronger than inductive electron-withdrawing. Due to the electronegativity, halogens are weak electron-withdrawing groups. Thus, moderate yields of seven-membered ring products were observed.

In short, seven-membered ring formation prevails when there is a weak electron-withdrawing group at the *para* position of salicylic ring (R) and strong electron-donating group substituent at the *para* position of benzylidene ring (Ar).

4.4 Isolation of Intermediate 81

Fortunately, we were able to isolate the intermediate **81** (Figure 4.1) in this one-step intramolecular cyclization of **51aa** which provided useful insights into the mechanism of cyclization.

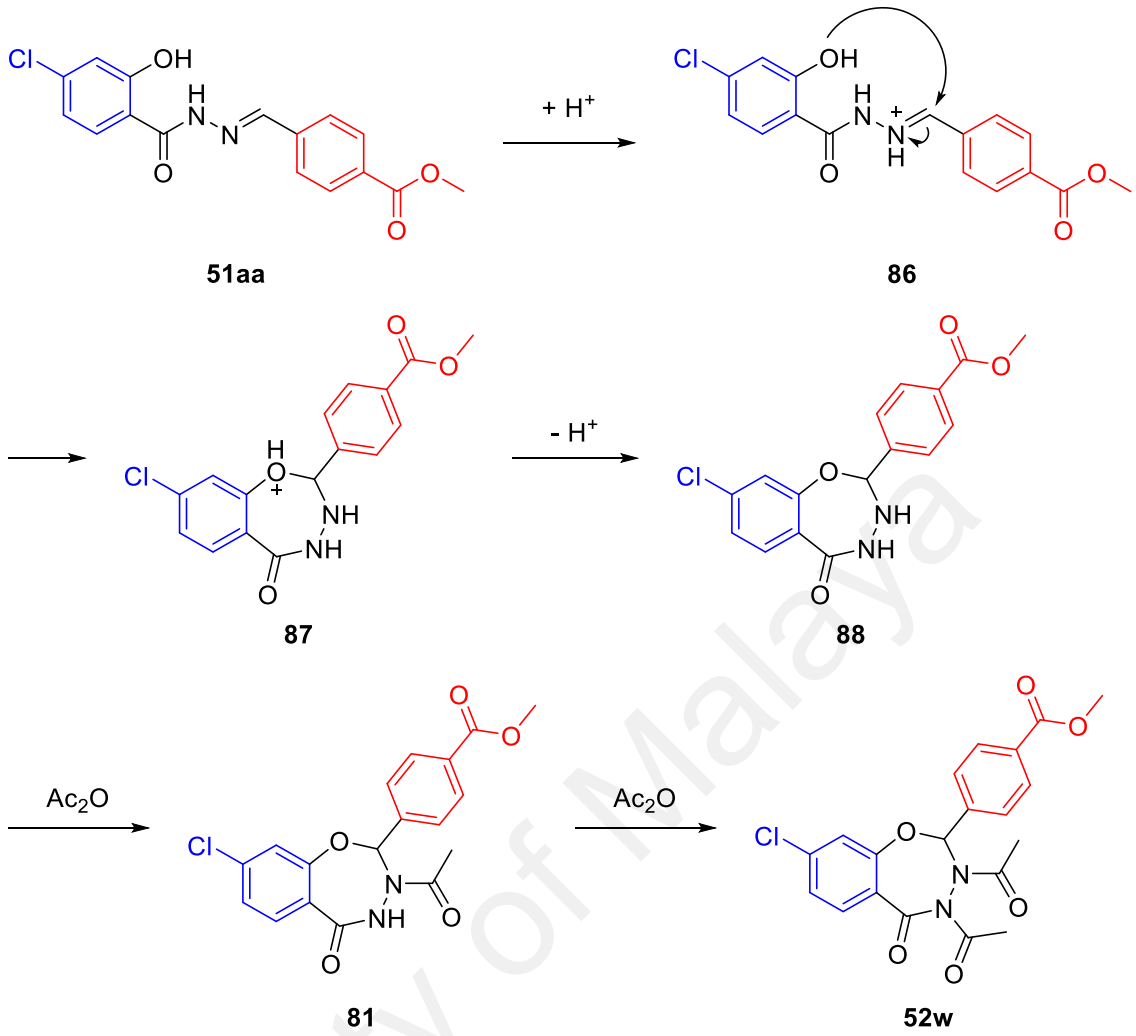


81

Figure 4.4. Structure of intermediate **81**.

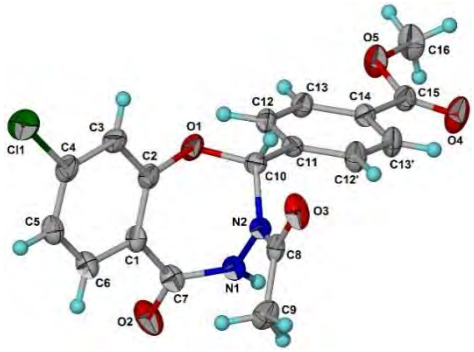
4.5 Plausible Mechanism

Based on the above experimental results and previous report (Alhadi *et al.*, 2015), a plausible mechanism for the synthesis of benzo-1,3,4-oxadiazepine is proposed as in Scheme 4.1. It involved an intramolecular cyclization of **51aa** which was initially protonated by the acid in the reaction medium to form the iminium ion **86**. Intramolecular nucleophilic attack of **86** by the hydroxy group resulted in the formation of an intermediate **87** which was deprotonated to give **88**. The acetylation of **88** form **81** which underwent further acetylation to form the final compound **52w**. The structure of intermediate **81** and product **52w** were further determined by X–ray crystallographic analysis (Tables 4.6 and 4.7).



Scheme 4.2. A proposed mechanism for the synthesis of **52w** through the intramolecular cyclization of **51aa.**

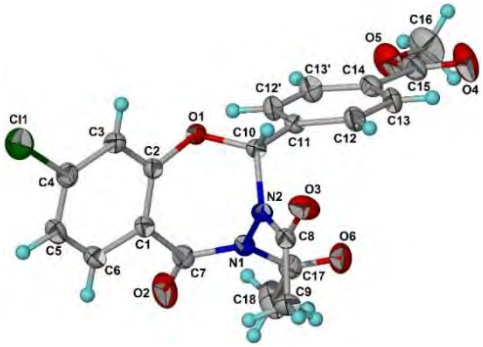
Table 4.6. Crystal data and structure refinement for **81**.



81 (CCDC No. 1815270)
The thermal ellipsoids are shown at the 50% probability level

Molecular formula	$C_{18}H_{15}ClN_2O_5$
Molecular weight, M_r	374.77
Melting point	175 – 180 °C
Temperature during diffraction experiment, T	180(3)
X-ray source	Mo K_α (λ = 0.71073)
Crystal system	Monoclinic
Space group	$P2_1/c$
a	5.8079(4) Å
b	13.8676(11) Å
c	21.4243(19) Å
α	90°
β	86.305(8) °
γ	90°
Volume, V	1931.7(3) Å^3
No. of molecule per unit cell, Z	4
Density (calcd)	1.446 g/cm^3
μ	0.255 mm^{-1}
F(000)	776
Crystal size	0.5 × 0.4 × 0.3 mm
2θ range for data collection	7.004 to 59.408°
Index ranges	$-7 \le h \le 7$, $-19 \le k \le 19$, $-29 \le l \le 29$
Reflections collected	15424
Independent reflections	4354 [R_{int} = 0.0231, R_{sigma} = 0.0212]
Data/restraints/parameters	4354/0/241
Goodness-of-fit on F^2	1.026
Final R indexes [$I \ge 2\sigma(I)$]	R_1 = 0.0408, wR_2 = 0.1035
Final R indexes [all data]	R_1 = 0.0520, wR_2 = 0.1126
Largest diff. peak/hole / e Å^{-3}	0.97/–0.49

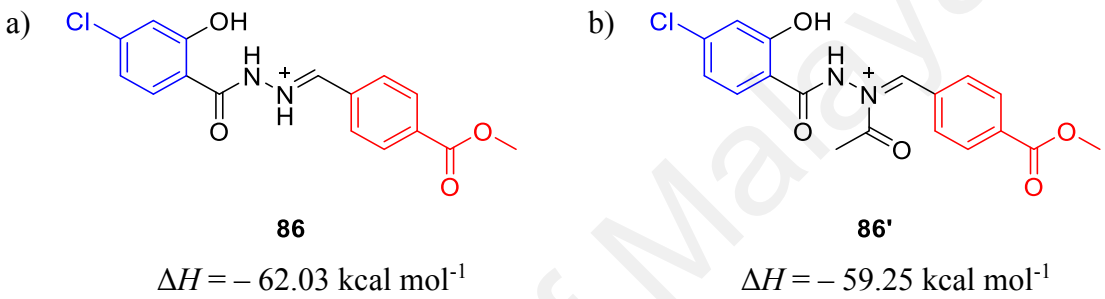
Table 4.7. Crystal data and structure refinement for **52w**.



52w (CCDC No. 1815271)
The thermal ellipsoids are shown at the 50% probability level

Molecular formula	$C_{20}H_{17}ClN_2O_6$
Molecular weight, M_r	416.80
Melting point	186 – 189 °C
Temperature during diffraction experiment, T	180(3)
X-ray source	Mo K_α (λ = 0.71073)
Crystal system	Monoclinic
Space group	$P2_1/c$
a	14.9816(12) Å
b	7.8080(6) Å
c	16.5697(11) Å
α	90°
β	94.717(6) °
γ	90°
Volume, V	1931.7(3) $Å^3$
No. of molecule per unit cell, Z	4
Density (calcd)	1.433 g/cm^3
μ	0.239 mm^{-1}
F(000)	864
Crystal size	0.5 × 0.4 × 0.2 mm
2θ range for data collection	7.05 to 59.508°
Index ranges	$-20 \le h \le 19$, $-10 \le k \le 10$, $-23 \le l \le 21$
Reflections collected	32254
Independent reflections	5108 [R_{int} = 0.0418, R_{sigma} = 0.0213]
Data/restraints/parameters	5108/0/265
Goodness-of-fit on F^2	1.106
Final R indexes [$I \ge 2\sigma(I)$]	R_1 = 0.0420, wR_2 = 0.1091
Final R indexes [all data]	R_1 = 0.0572, wR_2 = 0.1200
Largest diff. peak/hole / e $Å^{-3}$	0.97/–0.49

We have also considered the acetyliminium ion-mediated reaction mechanism. To understand this further, we compared the formation energy between iminium ion **86** (Figure 4.2a) and acetyliminium ion **86'** (Figure 4.2b) calculated based on the PM3 semi-empirical method using HyperChem 8.0 (Hypercube Inc.). The results revealed that **86** has a lower formation energy ($\Delta H = -62.03$ kcal mol^{-1}) as compared to **86'** ($\Delta H = -59.25$ kcal mol^{-1}), indicating that the reaction mechanism may preferably go through the iminium ion-mediated reaction mechanism.



86 $\Delta H = -62.03$ kcal mol^{-1}

86' $\Delta H = -59.25$ kcal mol^{-1}

Figure 4.5. Structures of a) iminium ion **86**; and b) acetyliminium ion **86'** with their respective calculated formation energies (ΔH) using PM3 semi-empirical method.

CHAPTER 5: CONCLUSION AND FUTURE STUDIES

5.1 Conclusion

In this study, a total of 30 *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepine derivatives (**52a-b, e-af**) were successfully synthesized through one-step intramolecular cyclization of variety *N*-(2-hydroxybenzoyl)hydrazones (**51a-b, e-an**) in the presence of 4.50% (*v/v*) of sulfuric acid and acetic anhydride as acylating agent with percentage yield of product ranging from 12 to 83%. These new class of heterocyclic compounds were characterized using the spectroscopic techniques such as NMR as well as through their melting point and molecular mass via HRMS (ESI). A reaction mechanism was proposed.

It was observed that when weak electron-withdrawing group is at the *para* position of salicylic ring and electron-donating group at the *para* position of benzylidene ring, good yield of seven-membered benzoxadiazepines was obtained.

5.2 Future Studies

Although the method for synthesis of benzo-1,3,4-oxadiazepine is developed, there are some *N*-(2-hydroxybenzoyl)hydrazones with strong electron-withdrawing group (**51m**, **51t**, **51u**, **51w**, **51ab**, **51ac**, **51ah** and **51am**) which have failed to cyclize into seven-membered ring. Hence, another synthesis method should be developed for the preparation of these compounds.

Further studies on the enantioselective synthesis on benzo-1,3,4-oxadiazepine can be investigated. Moreover, the synthesis of benzo-1,3,4-thiazepines and benzo-1,3,4-triazepines can also be carried out. Exploration of their biological potential such as hepatitis C protease and dengue virus protease can also be performed.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

1. **Chan, P. Q.**, Lee, Y. K., & Rahman, N. A. (2018). Facile intramolecular cyclization of *N*-(2-hydroxybenzoyl)hydrazones to *N*,*N*'-diacetyl benzo-1,3,4-oxadiazepine derivatives. *Asian Journal of Organic Chemistry, 7*(4), 707-710.

Presentation at the following conferences:

1. Oral presentation, "Synthesis of Benzoxadiazepines and Its Potential Biological Activity towards HCV Protease", The 7th Junior International Conference on Cutting-edge Organic Chemistry in Asia (Junior ICCEOCA-7)/ The 3rd Junior Advanced Researched Network on Cutting-edge Organic Chemistry in Asia (Junior ARNCEOCA-3), Lanzhou (China), October 30 - November 1, 2017.
2. Poster presentation, "Synthesis of The Potential Biologically Important Compounds of *N*-*N*'-Disubstituted Dibenzo-1,3,4-oxadiazepines", The 6th Junior International Conference on Cutting-edge Organic Chemistry in Asia (Junior ICCEOCA-6)/ The 2nd Junior Advanced Researched Network on Cutting-edge Organic Chemistry in Asia (Junior ARNCEOCA-2), Fukuoka (Japan), October 24 - 26, 2016.