Annexure - III

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

STATEMENT OF EXPENDITURE IN RESPECT OF MAJOR RESEARCH PROJECT

1. Name of Principal Investigator: Prof. Kamal K. Kapoor

2. Dept. of Principal Investigator: Department of Chemistry

3. University/College: University of Jammu

4. UGC approval Letter No. and Date: F.No.43-193/2014(SR) dated 30.10.2015

5. Title of the Research Project : Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation .

6. Effective date of starting the project: Sanctioned: 01.07.2015

7. a. Period of Expenditure: 01-07-2015 to 30-06-2018

b. Details of Expenditure

Name of the item	Amount Approved (Rs.)	Expenditure incurred (Rs.)
Books &Journals	0/-	0/-
Equipment	4,50,000/-	Nil
Contingency	90,000/-	**44,996 /-**
Field Work/Travel	45,000/-	**16,688 /-**
Hiring Services	0/-	0/-
Chemicals/Glassware	3,00,000/-	**1,50,000/-**
Overhead	96,600/-	**95,853 /-**
Total	9,81,600/-	**3,07,537/-**

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

J. C. Gupta & Co.
FRN - 001198 N
Jammu
Chartered Accountants

c. Staff

Date of appointment: (i) Dilpreet Kour : 15-03-2016 (Resigned on 31st Jan 2017)
(ii) Sheena Mahajan : 01-02-2017 (Resigned on 17th Oct 2017)

S.No	Items	From	To	Amount Approved (Rs.)	Expenditure incurred (Rs.)
1.	Honorarium to PI (Retired Teachers) @ Rs. 18,000/-p.m.				
2.	**Project fellow:** i) **NET/GATE qualified-** Rs. 16,000/- p.m. for initial 2 years and Rs. 18,000/- p.m. for the third year. ii) **Non-GATE/Non-NET-** Rs. 14,000/- p.m. for initial 2 years and Rs. 16,000/- p.m. for the third year.	15-03-2016	16-10-2017	5,76,000/-	**2,88,000/-**

1. It is certified that the appointment have been made in accordance with the terms and conditions laid down by the commission.
2. If as a result of check or audit objection some irregularity is noticed at later date, action will be taken to refund, adjust or regularize the objected amounts
3. Payment @ revised rates shall be made with arrears on the availability of additional funds.
4. It is certified that **Rs. 5,95,537/- (Rs. Five lakh ninety-five thousand five-hundred and thirty-seven only)** out of the total grant of **Rs. 10,52,100/- (Rs. Ten lakh fifty--two Thousand One Hundred Only) released as Ist instalment** for the years **2015-16 out of the Amount Approved = Rs. 15,57,600/- (Rs. Fifteen lakh fifty-seven thousand six hundred only)** received from University Grants Commission under the scheme for Major Research Project entitled "Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation ." vide UGC letter No. F.No.43-193/2014(SR) dated 30.10.2015 has been utilized for the purpose for which it was sanctioned with the terms and conditions laid down by University Grant.

20.08.2018

Signature of the Principal Investigator

Dr. Kamal K Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

Registrar
University of Jammu
Registrar

27/08/18

R. C. Gupta & Co.
FRN - 001198 N
Jammu
Chartered Accountants

Annexure - IV

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

STATEMENT OF EXPENDITURE INCURRED ON FIELD WORK

Name of the Principal Investigator: Prof. Kamal K. Kapoor

Name of the Place visited	Duration of the Visit		Mode of Journey	Expenditure Incurred (Rs.)
	From	To		
GNDU Amritsar (2-3rd) Feb, 2016	(a) Jammu (2nd Feb), 2016	Amritsar Jammu (2nd Feb), 2016	By own car	**4,270/-**
	(b) Amritsar (3rd Feb), 2016	Jammu (3rd Feb), 2016	By own car	
INSA New Delhi (22-24th) Feb, 2017	(a) Jammu Airport (22nd Feb), 2017	Delhi Airport (22nd Feb), 2017	By Air	**12,418/-**
	(b) Delhi Airport (22nd Feb), 2017	INSA Guest House (22nd Feb), 2017	By Taxi	
	(c) INSA Guest House (23rd Feb), 2017	Faridabad (23rd Feb), 2017	By OLA cab	
	(d) Faridabad (24th Feb), 2017	Airport (24th Feb), 2017	By OLA cab	
	(e) Airport (24th Feb), 2017	Jammu Airport (24th Feb), 2017	By Air	
			Total	**16,688/-**

Certified that the above expenditure is in accordance with the UGC norms for Major Research Projects.

20.08.2018

SIGNATURE OF PRINCIPAL INVESTIGATOR

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

Registrar

REGISTRAR
(Seal)

27/08/18

R. C. Gupta & Co.
FRN - 001198 N
Jammu
Chartered Accountants

Annexure - V

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

Utilization Certificate

It is certified that the grant of **Rs. 5,95,537/- (Rs. Five lakh ninety-five thousand five-hundred and thirty-seven only)** out of the total grant of **Rs. 10,52,100/- (Rs. Ten lakh fifty-two thousand and one hundred only) released as Ist instalment** for the years **2015-16 out of the Amount Approved = Rs. 15,57,600/- (Rs. Fifteen lakh fifty-seven thousand six hundred only)** received from University Grants Commission under the scheme for Major Research Project entitled "Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation." vide UGC letter No. F . 43-193/2014(SR) dated 30-10-2015 has been utilized during the period from 01-07-2015 to 30-06-2018 for the purpose for which it was sanctioned with the terms and conditions laid down by University Grant.

20.08.2018

Principal Investigator

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

Registrar
University of Jammu
27/08/18

Registrar

R. C. Gupta & Co.
CA
FRN - 001198 N
Jammu
Chartered Accountants

Statutory Auditor

M. No. 504307

Annexure-VI

PROFORMA FOR SUPPLYING THE INFORMATION IN RESPECT OF THE STAFF APPOINTED UNDER THE SCHEME OF MAJOR RESEARCH PROJECT

UGC FILE NO. : F-43-193/2014 (SR) Dated 30-10-2015

YEAR OF COMMENCEMENT: 15-03-2016

TITLE OF THE PROJECT: "Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation ."

1.	**Name of the Principal Investigator**	Prof. Kamal K.Kapoor				
2.	**Name of the University**	Department of Chemistry, University of Jammu.				
3A.	**Name of the Research Personnel appointed**	Ms. Sheena Mahajan From 01-02-2017				
4A.	**Academic Qualificaton**	**S No.**	**Qualifications**	**Year**	**Marks**	**%age**
		1.	M.Sc.	2009-2011		**72.98**
		2.	Ph.D	Pursuing as a full time research scholar		
5.	**Date of Joining**	01-02-2017				
6.	**Date of Birth of Research Personnel**	01-08-1988				
7.	**Amount of HRA, if Drawn**	NIL				
8.	**Number of candidates applied for the post**	8				

CERTIFICATE

This is to certify that all the rules and regulations of UGC Major Research Project outlined in the guidelines have been followed. Any lapse on the part of the University will liable to terminate of said UGC Project.

20.08.2018

Principal Investigator

21.08.2018

Head of the Deptt.

Registrar/Principal

Registrar
University of Jammu

27/08/18

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

Head,
Department of Chemistry,
University of Jammu, Jammu

C. Gupta & Co.
FRN - 001198 N
Jammu
Chartered Accountants

Month- Wise detailed statement of expenditure towards salary and HRA of project fellow

UGC Reference No. & Date : **F.No.43-193/2014(SR) dated 30.10.2015**

Name of the Project Fellow : **(a) Dilpreet Kour** **Date of joining** : **15-03-2016** (resigned on 31st Jan 2017)
(b) Sheena Mahajan **01-02-2017** (resigned on 17th Oct 2017)

S.No.	Month	Due		Drawn		Difference	
		Salary (in Rs.) /month	HRA	Salary (in Rs.) /month	HRA	Salary (in Rs.)	HRA
1	March, 2016	8774/=	NIL	8774/=	NIL	0	NIL
2	April, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
3	May, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
4	June, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
5	July, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
6	August, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
7	September, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
8	October, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
9	November, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
10	December, 2016	16,000/=	NIL	16,000/=	NIL	0	NIL
11	January, 2017	16,000/=	NIL	16000/=	NIL	0	NIL
12	February, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
13	March, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
14	April, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
15	May, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
16	June, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
17	July, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
18	August, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
19	September, 2017	14,000/-	2,800/-	14,000/-	NIL	0	2,800/-
20	October, 2017	14,000/-	1,445/-	7,226/-	NIL	6,774	1,445/-
Total		**2,94,774/**	**23,845/-**	**2,88,000/-**	**0**	**6,774**	**23,845/-***

*** HRA for the amount of Rs. 23,845 to be claimed for the Salary @ Rs. 14000 w.e.f 01.02.2017 to 16.10.2018.**

Principal Investigator
Department of Chemistry
University of Jammu

Signature of Principal Investigator

R.C. Gupta & Co. FRN - 001198 N Jammu Chartered Accountants

Registrar
Jammu

Registrar
(Seal & Signature)

12/9/18

PROJECT REPORT

Vide No. MRP-MAJOR-CHEM-2013-21745 dated 30.10.2015

Title of the Project:

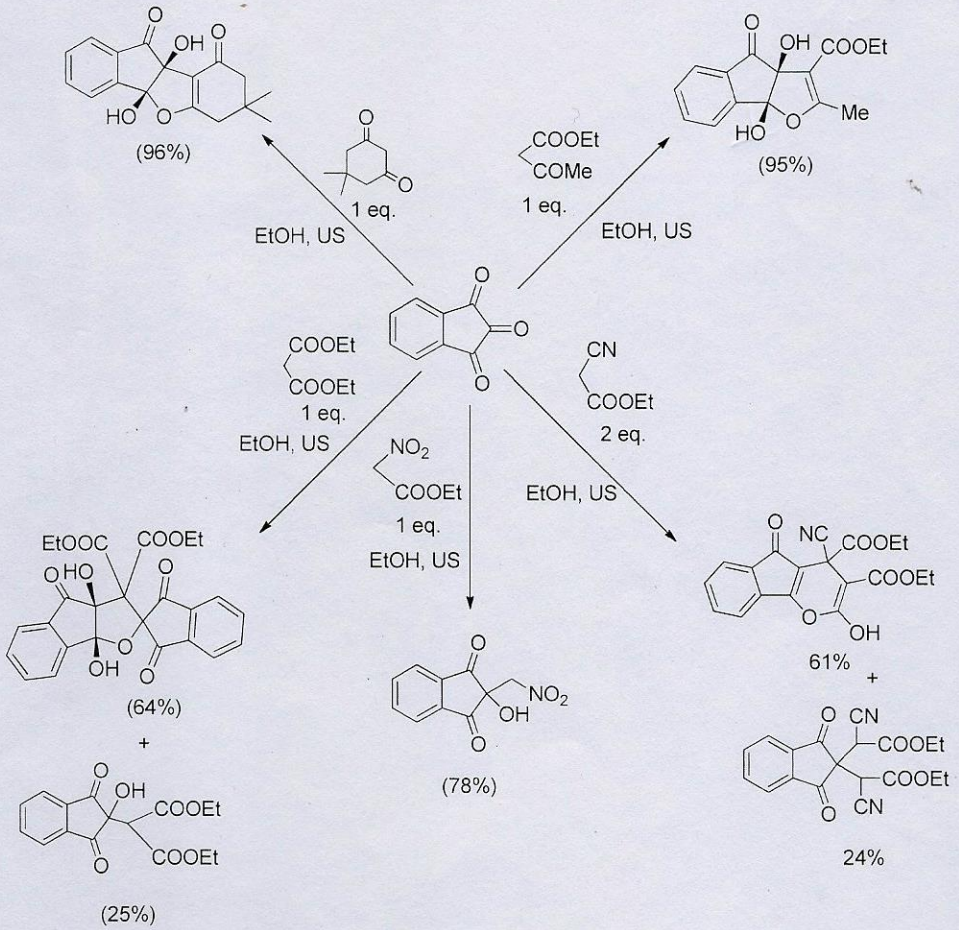
Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation

Experimental Outcome:

A. Synthesis of various fused and spiro oxygen-heterocycles (indenopyran, spiroindenopyran, indenofuran and spiroindenofuran derivatives)

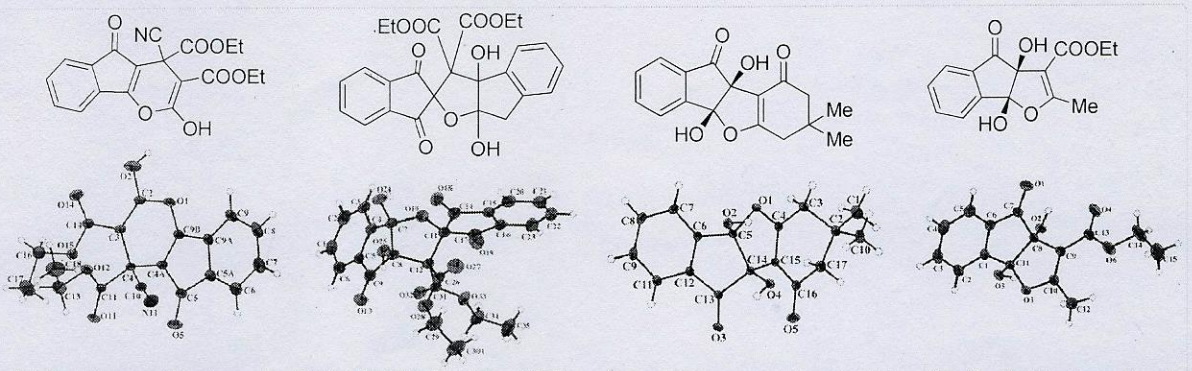
An unprecedented synthesis of various fused and spiro oxygen-heterocycles (indenopyran, spiroindenopyran, indenofuran and spiroindenofuran derivatives) has been achieved from Aldol and Knoevenagael products of ninhydrin and active methylenes without the use of any additives under ultrasonic irradiation **(Scheme 1)**.

Scheme 1: Ultrasonic-assisted reaction of ninhydrin with different active methylenes.



All products have been characterized by spectral data [^{1}H NMR, ^{13}C NMR, IR and HRMS] as well as X-ray diffraction studies of some compounds obtained as single crystals.

ORTEP diagrams of some products:



Diethyl-4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-b]pyran-3,4-dicarboxylate

Diethyl 3a',8a'-dihydroxy-1,3,8'-trioxo-1,3,8',8a'-tetrahydrospiro [indene-2,2'-indeno[2,1-b]furan]-3',3'(3a'*H*)-dicarboxylate)

4b,9b-dihydroxy-7,7-dimethyl-7,8-dihydro-4b*H*-indeno[1,2-b]benzo furan-9,10(6*H*,9b*H*)-dione

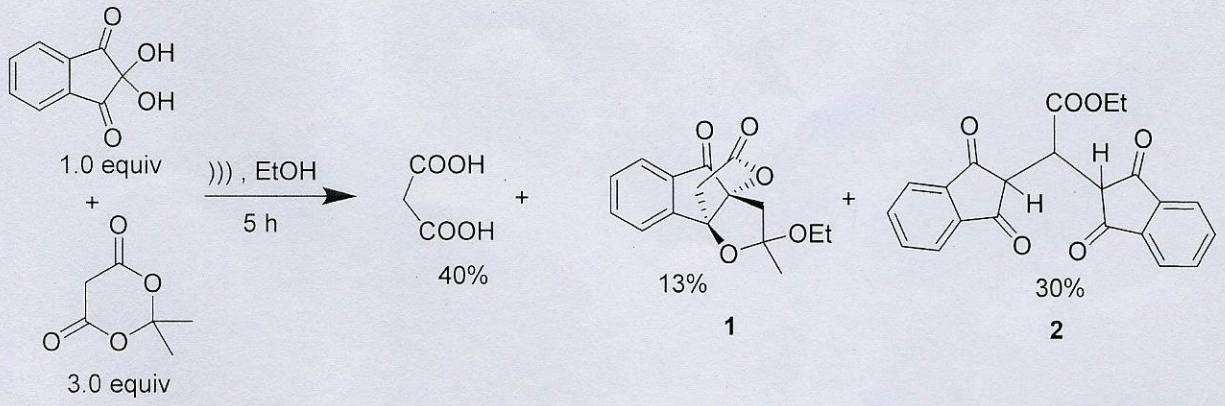
Ethyl 3a,8b-dihydroxy-2-methyl-4-oxo-4,8b-dihydro-3a*H*-indeno [1,2-b]furan-3-carboxylate

Details (genesis, optimisation, results and discussion, experimental and characterizations) are given in attached publication. [*Tetrahedron*, **2016**, *72*, 257-263]

B. Synthesis of novel [3.3.3] propellanoid *viz.* 2-ethoxy-2-methyl-2*H*-3a,8b-(epoxyethano)indeno[1,2-*b*]furan-4,10(3*H*)-dione and ethyl 2,2-bis(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate

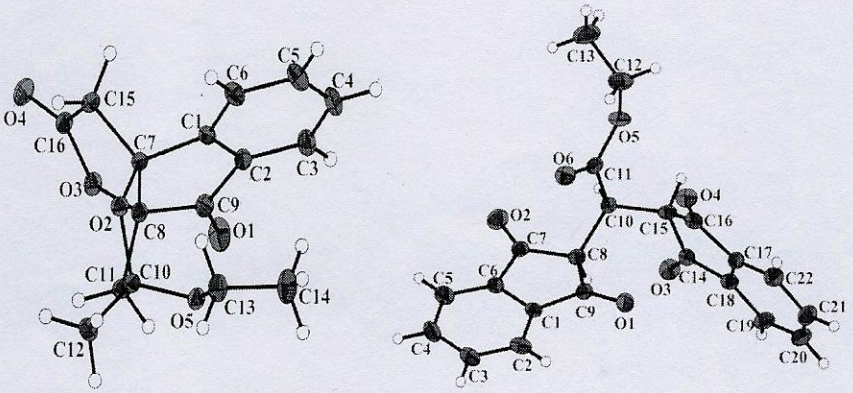
A novel [3.3.3] propellanoid *viz.* 2-ethoxy-2-methyl-2*H*-3a,8b-(epoxyethano)indeno[1,2-*b*]furan-4,10(3*H*)-dione **1** and ethyl 2,2-bis (1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate **2** were obtained by the reaction of ninhydrin with Meldrum's acid under ultrasonic-irradiation in ethanol **(Scheme 2)**.

Scheme 2: Synthesis of 2-ethoxy-2-methyl-2*H*-3a,8b-(epoxyethano)indeno[1,2-*b*]furan-4,10(3*H*)-dione and ethyl 2,2-bis(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate.



{Unpublished result}

ORTEP diagram showing molecular structure of 2-ethoxy-2-methyl-2*H*-3a,8b-(epoxyethano)indeno[1,2-*b*]furan-4,10(3*H*)-dione 1 and ethyl 2,2-bis(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetate 2 :



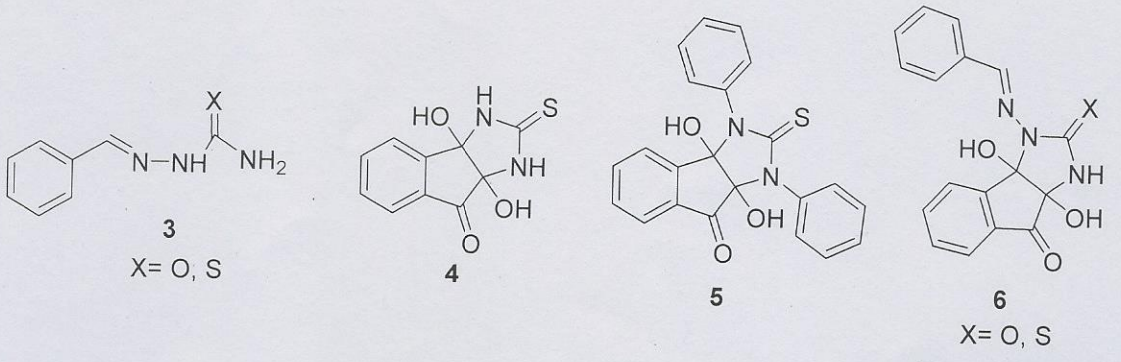
1 **2**

C. Synthesis of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and their 2-thioxo analogues

The anti-microbial properties associated with hydrazones (semicarbazones and thiosemicarbazones) **3** and tetrahydroindeno[1,2-*d*]imidazol-8*(2H)*-one and its diphenyl derivatives led us to design hybrid molecules possessing the attributes of hydrazones as well as tetrahydroindeno[1,2-*d*]imidazolones.

Compound **4** obtained by the reaction of ninhydrin with thiourea, exhibited promising anti-microbial activity against gram positive and gram negative bacteria and a fungus *Candida albicans* (Ghalib et al., 2011). Compound **5**, a hydrophobic analogue of **4** is devoid of two H-bond donors. Obtained (Ghalib et al., 2012) by the reaction of ninhydrin with diphenyl thiourea, compound **5** has shown improvement in activity against some bacterial stains (*Bacillus subtilis, Streptococcus pneumoniae, Pseudomonas aeruginosa*) and loss against some other strains (*Shigella flexneri, Escherichia coli*). Loss in anti-fungal activity of compound **5** against *C. albicans* was also noticed (Ghalib et al., 2011; Ghalib et al., 2012). In view of this irregular trend in activity, we wished to maintain a balance between hydrophilicity and hydrophobicity by retaining one H-bond donor and this led us to design a compound **6** possessing the attributes of hydrazones as well as tetrahydroindeno[1,2-*d*]imidazolones **(Figure 1)**.

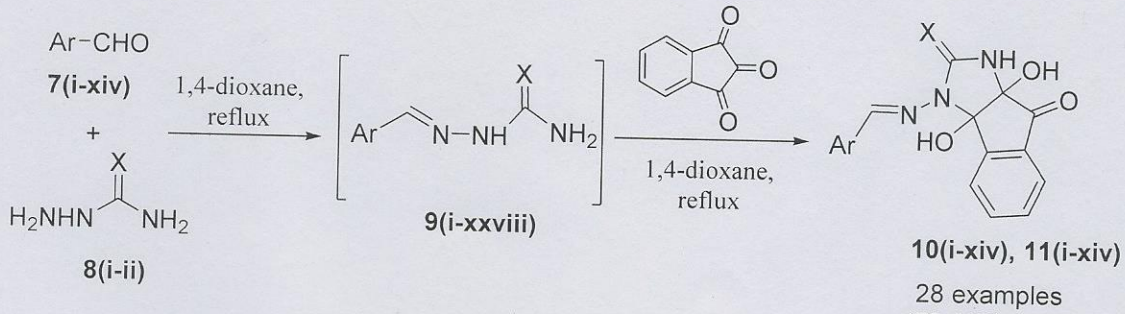
Figure 1 : Design of prototype



To achieve this goal, following protocol was conceived:

A series of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydro indeno[1,2-*d*]imidazol-8(*2H*)-ones have been synthesized *via* one-pot, catalyst-free reaction of aldehydes, semicarbazide hydrochloride/thiosemicarbazide with ninhydrin **(Scheme 3)** and screened for anti-microbial activity. The synthesized compounds were observed to possess broad spectrum; antibacterial potential as well as significant antagonistic potential against fungal pathogens.

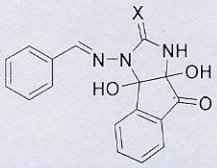
Scheme 3 : Synthesis of 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydro indeno[1,2-*d*]imidazol-8(*2H*)-ones



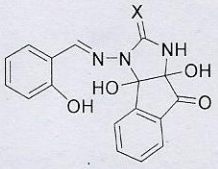
X = O, S

Ar = C_6H_5, 2-OH-C_6H_4, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 3-CH_3O-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4, 4-Br-C_6H_4,4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 3,4,5-$(CH_3O)_3$-C_6H_4,1-napthyl, furan-2-carbyl, 6-bromobenzo[*d*][1,3]dioxole-5-carbyl.

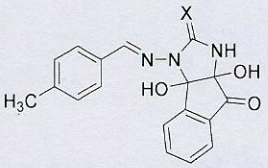
Substrate scope :



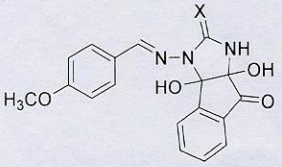
X = O, 10(i) [90%; 120(30,90)]*
X = S, 11(i) [87%; 135(35,100)]*



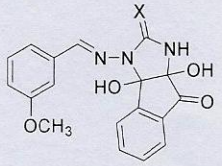
X = O, 10(ii) [88%; 100(30,70)]*
X = S, 11(ii) [86%; 90(40,50)]*



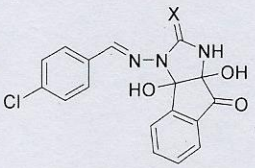
X = O, 10(iii) [80%; 140(40,100)]*
X = S, 11(iii) [80%; 185(45,140)]*



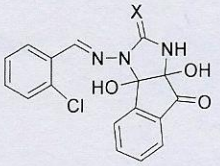
X = O, 10(iv) [92%; 112(32,80)]*
X = S, 11(iv) [82%; 175(35,140)]*



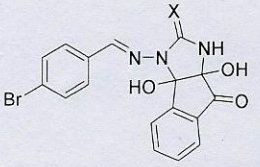
X = O, 10(v) [90%; 120(30,90)]*
X = S, 11(v) [84%; 155(30,120)]*



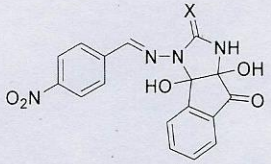
X = O, 10(vi) [90%; 100(30,70)]*
X = S, 11(vi) [86%; 85(25,60)]*



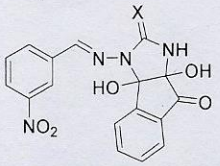
X = O, 10(vii) [92%; 115(35,80)]*
X = S, 11(vii) [81%; 135(35,100)]*



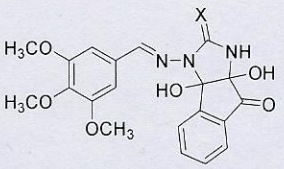
X = O, 10(viii) [83%; 160(40,120)]*
X = S, 11(viii) [78%; 200(60,140)]*



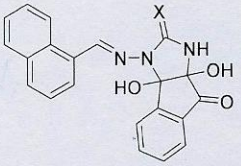
X = O, 10(ix) [84%; 155(45,110)]*
X = S, 11(ix) [82%; 170(50,120)]*



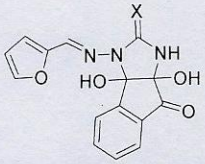
X = O, 10(x) [81%; 145(35,110)]*
X = S, 11(x) [80%; 175(55,120)]*



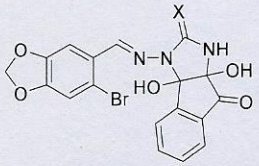
X = O, 10(xi) [92%; 110(30,80)]*
X = S, 11(xi) [80%; 190(60,130)]*



X = O, 10(xii) [92%; 105(35,70)]*
X = S, 11(xii) [88%; 80(30,50)]*

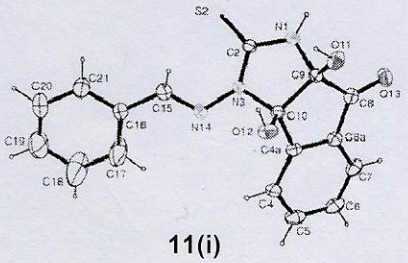


X = O, 10(xiii) [93%; 100(30,70)]*
X = S, 11(xiii) [85%; 100(35,65)]*



X = O, 10(xiv) [83%; 170(50,130)]*
X = S, 11(xiv) [83%; 200(60,140)]*

ORTEP diagram of 3-(benzylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-one 11(i):



11(i)

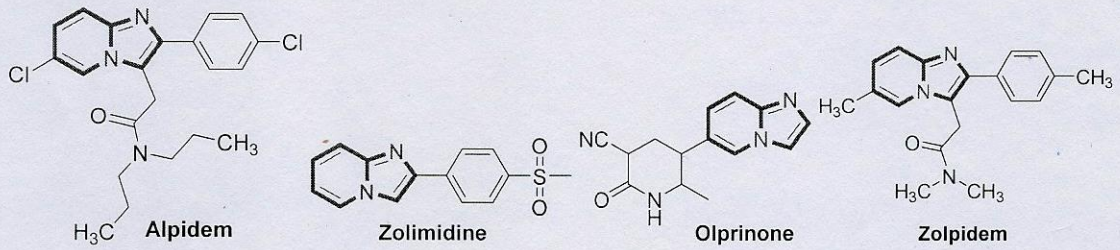
Twenty eight novel hybrid molecules *viz.* 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-diones and their 2-thioxo analogues have been synthesized *via* one-pot catalyst-free reaction of aldehydes, semicarbazide hydrochloride/thiosemicarbazide with ninhydrin using 1,4-dioxane as solvent. All the synthesized compounds are well supported by spectral data.

Details (genesis, optimisation, results and discussion, experimental and characterizations) are given in attached publication. [*Synth. Commun.*, **2017**, *72*, 1159-1168]

D. Synthesis of 2-arylimidazo[1,2-a]pyridines

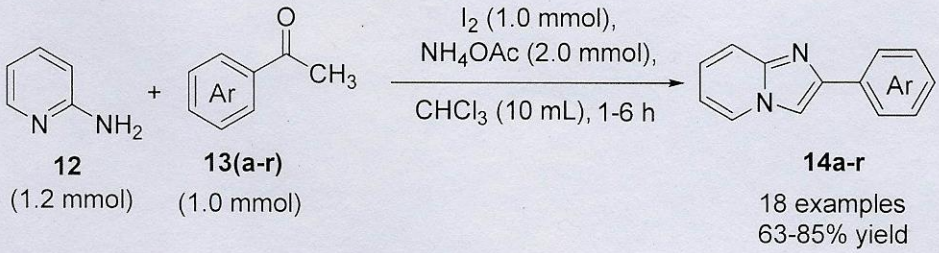
Imidazo[1,2-*a*]pyridines are indispensable biologically active nitrogen containing heterocyclic scaffolds and possess a wide range of biological activities such as anti-cancer,[1] anti-viral,[2] anti-inflammatory,[3] analgesic, anti-pyretic,[4] anti-ulcer[5] and anti-bacterial.[6] Imidazo[1,2-a] derivatives based prospective radio ligands for positron emission tomography (PET) for-amyloid in Alzheimer's disease have been widely reported.[7] They also act as GABA and benzodiazepine receptor agonists[8] and cardiotonic agents.[9] These structures are also found in clinical drugs such as alpidem,[10] zolpidem,[8] olprinone,[11] zolimidine[4] **(Figure 2)**.

Figure 2 : Bio-active drugs containing imidazo[1,2-*a*]pyridine scaffold

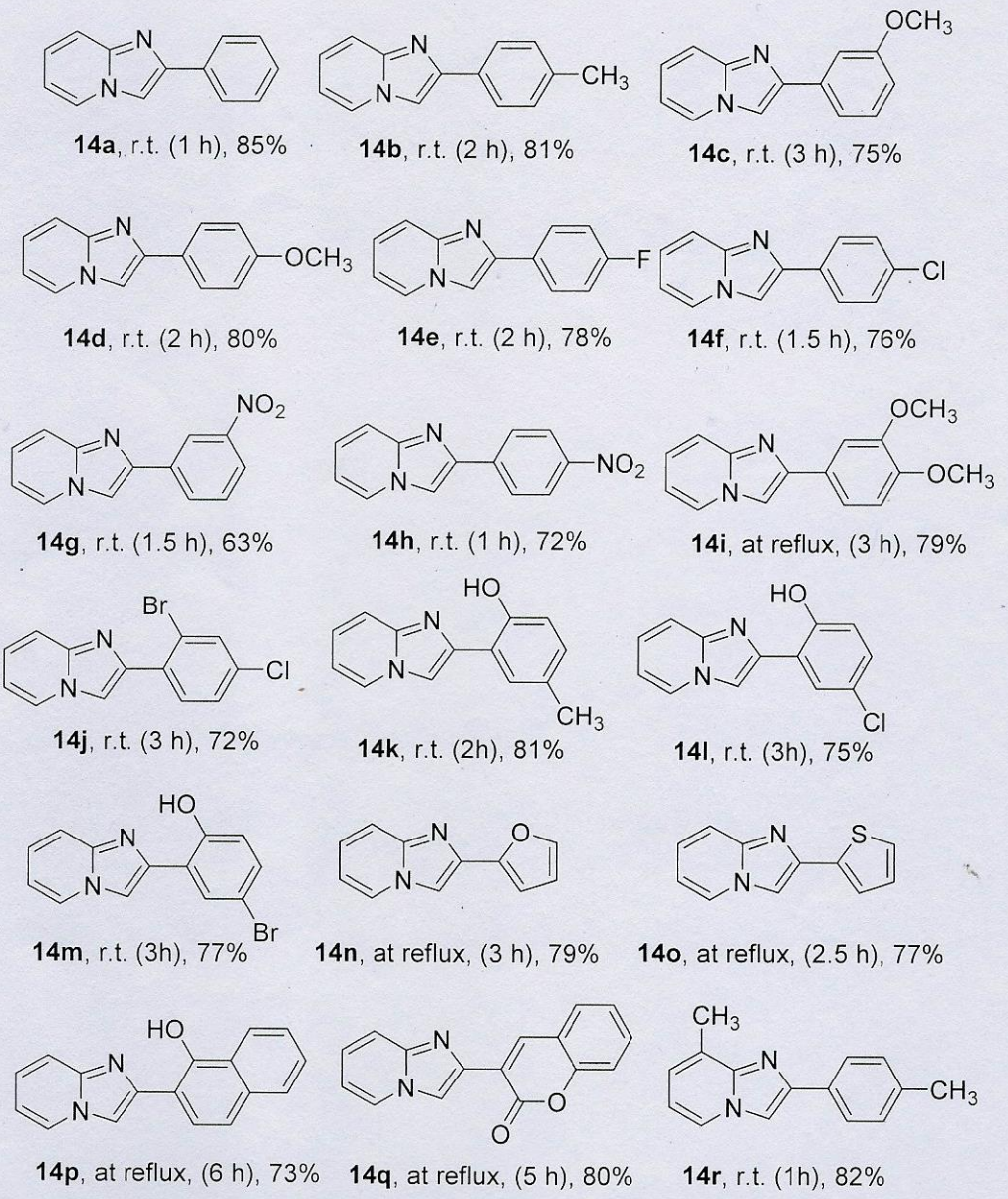


In addition to this, 2-(2-hydroxy phenyl)imidazo[1,2-a]pyridines exhibit excellent excited state intramolecular proton transfer (ESIPT)[12] thereby embracing significance in the field of optoelectronics. Owing to the attractive properties of imidazo[1,2-a]pyridines, a protocol involving I_2–NH_4OAc promoted one-pot metal-free synthesis of diversely substituted imidazo[1,2-a]pyridines **14a-r** from 2-aminopyridine **12** and aryl methyl ketones **13a-r** was established **(Scheme 4)**. 2-Arylimidazo[1,2-a]pyridines **14a–r** were obtained in good to excellent yields *via* in situ generation of an Ortoleva–King intermediate (pyridinium iodide), followed by NH_4OAc-assisted cyclization.

Scheme 4 : I_2–NH_4OAc promoted synthesis of imidazo[1,2-a]pyridines **14a-r**



Substrate Scope



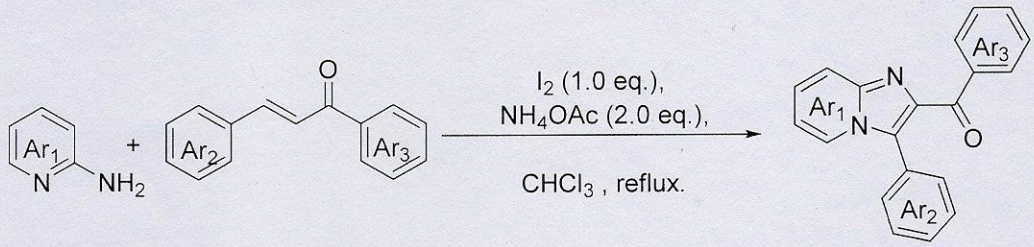
Details (genesis, optimisation, results and discussion, experimental and characterizations) are given in attached publication. [*Tetrahedron Lett.*, **2016**, *57*, 4464-4467]

E. Synthesis of 2-aroyl-3-arylimidazo[1,2-a]pyridines

Various analogues of imidazopyridine have been synthesized[13] and among them, aroylimidazo[1,2-a]pyridines have emerged as the interesting structures since aroyl functionality has been found to be responsible for their elevated biological properties.[14] Nowadays, emphasis is on the development of metal-free synthetic protocols. In this perspective, an efficient, metal-free regioselective synthesis of 2-aroyl-3-arylimidazo [1,2-a]pyridines **15** from 1,3-diaryl-prop-

2-en-1-ones and 2-aminopyridine was achieved **(Scheme 5)**. The iodine–NH_4OAc promoted reaction offers a novel route in the synthesis of 2-aroyl-3-arylimidazo[1,2-a]pyridines. This protocol offers significant flexibility in accessing medicinally important 2-aroyl-3-arylimidazo[1,2-a]pyridines with various substitution patterns.

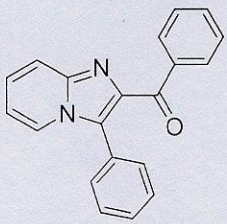
Scheme 5 : Synthesis of 2-aroyl-3-arylimidazo[1,2-a]pyridines[a,b]



15a-o

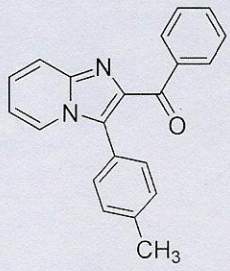
15 examples
72-85% yield

Substrate Scope



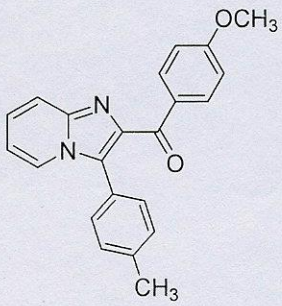
15a

(1hr), 85%



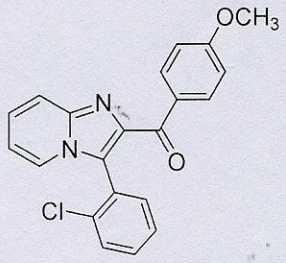
15b

(1hr), 83%



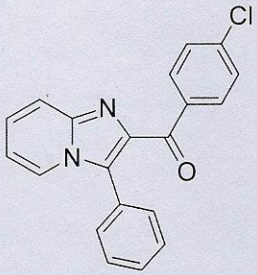
15c

(1.5hr), 85%



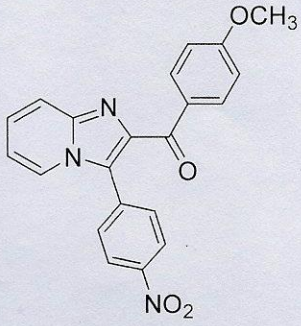
15d

(2 hr), 80%



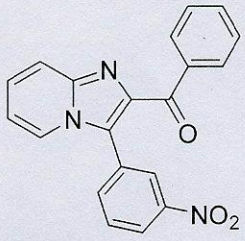
15e

(1.5 hr), 82%



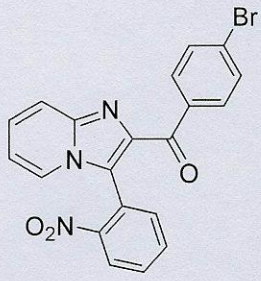
15f

(2 hr), 80%



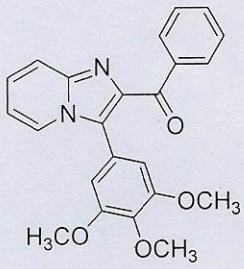
15g

(2 hr),79%



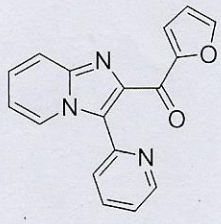
15h

(2 hr), 81%



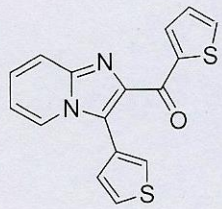
15i

(1 hr), 82%



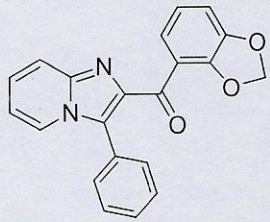
15j

(1.5 hr), 81%



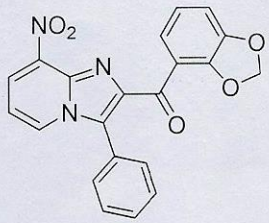
15k

(1.5 hr), 80%



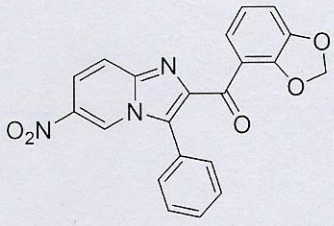
15l

(2 hr), 72%



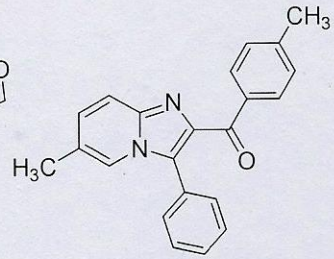
15m

(2 hr), 80%



15n

(2 hr), 78%

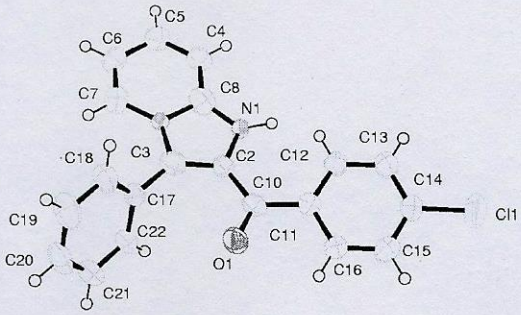


15o

(2 hr), 80%

[a] carried out with **1** (1.2 mmol), **2a** (1.0 mmol), iodine (1 mmol), NH_4OAc (2.0 mmol) in $CHCl_3$ (10 ml) under reflux; [b] isolated yields after column chromatography.

ORTEP of the compound 15e :



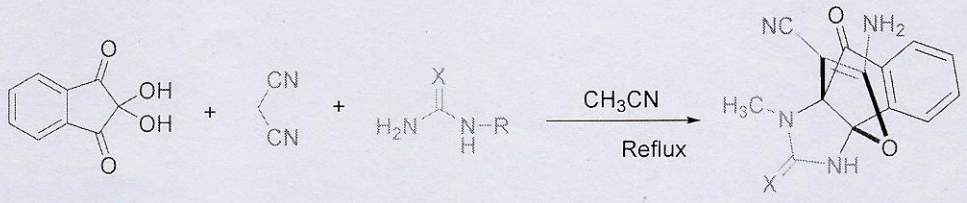
Details (genesis, optimisation, results and discussion, experimental and characterizations) are given in attached publication. [*Org. Biomol. Chem.*, **2018**, *16*, 1330-1336]

F. Synthesis of Indeno-fused [3.3.3]propellanes

A general strategy for the synthesis of novel indenofused heterocyclic motifs through one-pot multicomponent reaction between ninhydrin, malononitrile and various binucleophiles was developed (**Scheme 6** and **Scheme 7**).

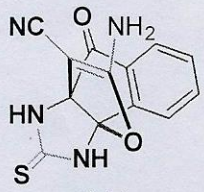
(a) Synthesis of Synthesis of furoindeno-imidazo[3.3.3]propellanes 16a-h

Scheme 6: Synthesis of furoindeno-imidazo[3.3.3]propellanes **16a-h** from ninhydrin, malononitrile and binucleophiles

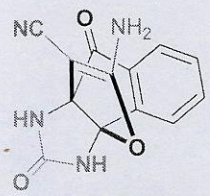


16a-h

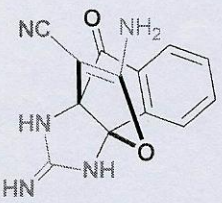
Substrate Scope



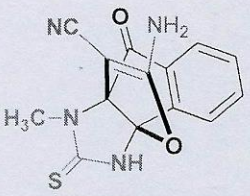
(16a)
30 min, 87%



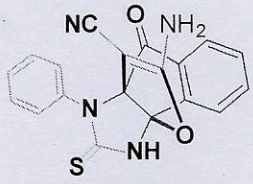
(16b)
40 min, 88%



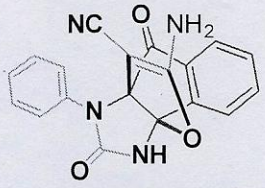
(16c)
25 min, 86%



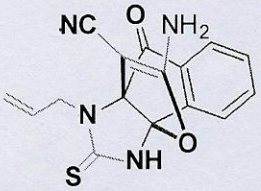
(16d)
30 min, 86%



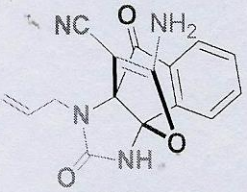
(16e)
45 min, 85%



(16f)
5hr, 82%



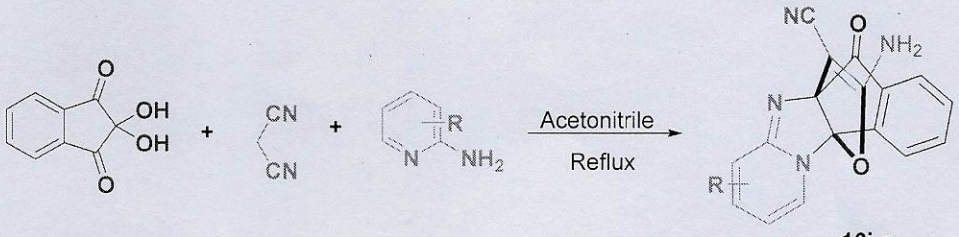
(16g)
30 min, 85%



(16h)
30 min, 85%

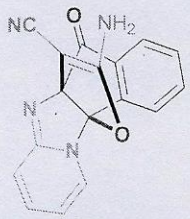
(b) Synthesis of furanoindenoimidazopyridine[3.3.3]propellanes 16i-p

Scheme 7: Synthesis of furanoindenoimidazopyridine[3.3.3]propellanes **16i-p** from ninhydrin, malononitrile and substituted 2-aminopyridines

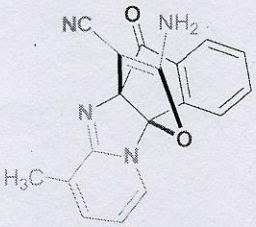


16i-p

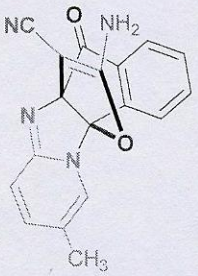
Substrate Scope



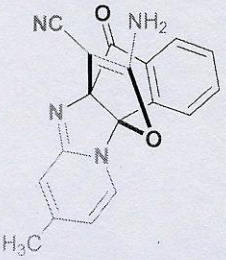
(16i)
20 min, 86%



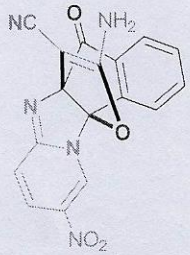
(16j)
15 min, 84%



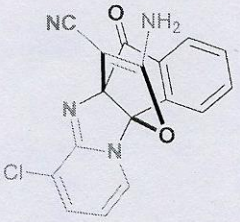
(16k)
15 min 86%



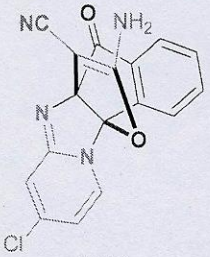
(16l)
15 min 84%



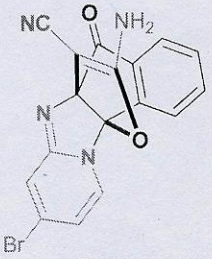
(16m)
30 min 80%



(16n)
20 min 80%



(16o)
15 min 85%



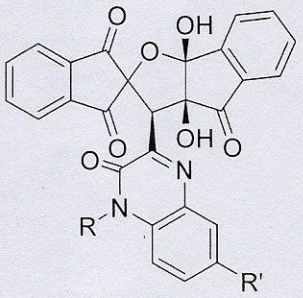
(16p)
20 min, 85%

All the synthesized compounds are well supported by spectral data (^{1}H &^{13}C NMR, IR and EIMS analysis).

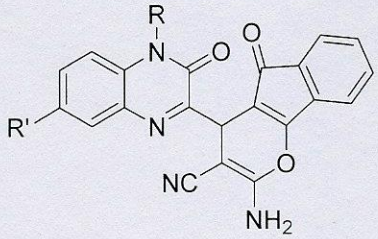
{Unpublished result}

G. Synthesis of Ninhydrin based spiro-fused heterocyclic scaffolds

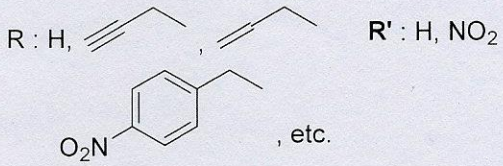
Quinoxaline represents a versatile class of nitrogen containing heterocyclic compounds of various biologically interesting properties with several pharmaceutical applications. Substituted quinoxalines constitute the building blocks of wide range of pharmacologically active compounds having anti-bacterial,[15] anti-fungal,[16] anti-cancer,[17] anti-tubercular,[18] anti-leishmanial,[19] anti-malarial[20] and anti-depressant activities.[21] Also, some quinoxaline-2-ones and quinoxaline-2,3-diones have been reported to show anti-microbial,[22] novel potent anti-thrombotic,[23] anti-pain and anti-inflammatory[24] activities. In addition to this, these serve as ligands in coordination.[25] Quinoxaline is a part of various antibiotics such as echinomycin, levomycin and actinoleutin, which are known to inhibit the growth of gram positive bacteria and are active against various transplantable tumors.[26] Due to interesting biological effects of quinoxaline and importance of ninhydrin as a building block in organic synthesis We successfully developed a versatile method for the preparation of derivatives of (3'R,3a'R,8b'R)-3a',8b'-dihydroxy-3'-(3-oxo-3,4-dihydroquinoxalin-2-yl)-3',3a'dihydrospiro[indene-2,2'-indeno[1,2-b]furan]-1,3,4'(8b'H)-triones **17** and 2-amino-5-oxo-4-(3-oxo-3,4-dihydroquinoxalin-2-yl)-4,5-dihydroindeno[1,2-b]pyran-3-carbonitriles **18** in good to excellent yields by the reaction of ninhydrin with methylquinoxalinones and its knoevenagel adducts respectively.



17



18



These are novel structures and diversely substituted analogs were prepared. All the products have been synthesized and they are characterized by using various spectral means (^{1}H &^{13}C NMR, IR and EIMS analysis).

{Unpublished result}

References

1. C. Hamdouchi, J. D. Blas, M. D. Prado, J. Gruber, B. A. Heinz, L. Vance, *J. Med. Chem.*, **1999**, *42*, 50.
2. A. Elkakmaoui, A. Gueiffier, J. C. Milhavet, Y. J. Blache, P. Chapat, O. Chavignon, J. C. Teulade, R. Snoeck, G. Andrei, E. D. Clerc, *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 1937.
3. R. B. Lacerda, C. K. F. de Lima, L. L. da Silva, N. C. Romeiro, A. L. P. Miranda, E. J. Barreiro, C. A. M. Fraga, *Bioorg. Med. Chem.*, **2009**, *17*, 74.
4. L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, W. Murmann, *J. Med. Chem.*, **1965**, *8*, 305.
5. J. J. Kaminski, A. M. Doweyko, *J. Med. Chem.*, **1997**, *40*, 427.
6. K. F. Byth, J. D. Culshaw, S. Green, S. E. Oakes, A. P. Thomas, *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 2245.
7. L. Cai, F. T. Chin, V.W. Pike, H. Toyama, J.S. Liow, S.S. Zoghbi, K. Modell, E. Briard, H.U. Shetty, K. Sinclair, S. Donohue, D. Tipre, M.P. Kung, C. Dagostin, D.A. Widdowson, M. Green, W. Gao, M.M. Herman, M. Ichise, R.B. Innis, *J. Med. Chem.*, **2004**, *47*, 2208.
8. A. C. Humphries, E. Gancia, M. T. Gilligan, S. Goodacre, D. Hallett, K.J. Merchant, S.R. Thomas, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1518.
9. D. Davey, P. W. Erhardt, W.C. Lumma, J. J. Wiggins, M. Sullivan, D. Pang, E. Cantor, *J. Med. Chem.* **1987**, *30*, 1337.
10. A. N. Jain, *J. Med. Chem.*, **2004**, *47*, 947.
11. K. Mizushige, T. Ueda, K. Yukiiri, H. Suzuki, *Cardiovasc. Drug Rev.*, **2002**, *20*, 163.
12. A. Douhal, F. A. Guerri, A. U. Acuna, *J. Phys. Chem.*, **1995**, *99*, 76.
13. (a) S. Kang, R. Y. Kim, M. J. Seo, S. Lee, Y. M. Kim, M. Seo, J. J. Seo, Y. Ko, I. Choi, J. Jang, J. Nam, S. Park, H. Kang, H. J. Kim, J. Kim, S. Ahn, K. Pethe, K. Nam, Z. No and J. Kim, *J. Med. Chem.*, **2014**, *57*, 5293; (b) N. Masurier, E. Debiton, A. Jacquemet, A. Bussiere, J. M. Chezal, A. Ollivier, D. Tetegan, M. Andaloussi, M. J. Galmier, J. Lacroix, D. Canitrot, J. C. Teulade, R. C. Gaudreault, O. Chavignon and E. Moreau, *Eur. J. Med. Chem.*, **2012**, *52*, 137; (c) A. R. Katritzky, M. Michalska, R. L. Harlow and S. H. Simonsen, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 354.
14. (a)C. E. Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.*, **2007**, *7*, 888; (b) L. Hu, J.-D. Jiang, J. Qu, Y. Li, J. Jin, Z.-R. Li and D. W. Boykin, *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 3613.
15. S. Ganapaty, P. Ramalingam and C.B. Rao, *Indian J. Heterocycl. Chem.*, **2007**, *16*, 283.
16. V.K. Tandon, D.B. Yadav, H.K. Maurya, A.K. Chaturvedi and P.K. Shukla, *Bioorg. Med. Chem.*, **2006**, *14*,

6120.
17. A. Carta, P. Sanna, Gherardini, D. Usai and S. Zanetti, *Farmaco.*, **2001**, *56*, 933.
18. A. Jaso, B. Zarranz, I. Aldana and A. Monge, *Eur. J. Med. Chem.*, **2003**, *38*, 791.
19. J. Guillon, I. Forfar, M.M. Matsuda, V. Desplat, M. Saliege and D. Thiolat, *Bioorg. Med. Chem. Lett.*, **2007**, *15*, 194.
20. J.B. Rangisetty, C.N.V.H.B. Gupta, A.L. Prasad, P. Srinivas, N. Sridhar, P. Parimoo and A. Veeranjaneyulu, *J. Pharm. Pharmaco.*, **2001**, *53*, 1409.
21. S.Y. Hassan, S.N. Khattab, A.A. Bekhit and A. Amer, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1753.
22. C.A. Obafemi and D.A. Akinpelu, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, **2005**, *180*, 1795.
23. U.J. Ries, H.W. Priekpe, N.H. Havel, S. Handschuh, G. Mihm, J.M. Stassen, W. Wienen and H. Nar, *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 2297.
24. D.S. Su and M.G. Bock, *US Patent. Appl.*, **2005**, 20050020591.
25. B.D. Glisic, B. Warzajtis, N.S. Radulovic, U. Rychlewska and M.I. Djuran, *Polyhedron*, **2015**, *87*, 208.
26. M.M. Heravi, K. Bakhtiari, M.H. Tehrani, N.M. Javadi and H.A. Oskooie, *ARKIVOC*, **2006**, *16*, 16.

(Principal Investigator)

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-MAJOR-CHEM-2013-21745
Department of Chemistry
University of Jammu

Registrar
University of Jammu

(Registrar / Principal)

Seal

Annexure – XI

Final Report Assessment / Evaluation Certificate
(Two Members Expert Committee Not Belonging to the Institute of Principal Investigator)
(to be submitted with the final report)

It is certified that the final report of Major Research Project entitled **"Unprecedented cascade reactions between ninhydrin and active methylenes: Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation"** by **Prof. Kamal K. Kapoor** Dept. of **Chemistry** has been assessed by the committee consisting the following members for final submission of the report to the UGC, New Delhi under the scheme of Major Research Project.

Comments/Suggestions of the Expert Committee:-

- Excellent piece of work resulting in the synthesis of architecturally challenging molecules
- PI is advised to extend this work to explore new vistas of ninhydrin scaffold.

Name & Signatures of Experts with Date:-

	Name of Expert	University/College name	Signature with Date
1.	T. Punniyamurthy	IIT Guwahati Professor and Head, Department of Chemistry	8/9/18
2.	Palwinder Singh Professor	Dept. of Chem. GNDU, Asr Amritsar	Palwinder Singh 8/9/18

It is certified that the final report has been uploaded on UGC-MRP portal on ..... .

It is also certified that final report, Executive summary of the report, Research documents, monograph academic papers provided under Major Research Project have been posted on the website of the University/College.

Registrar
University of Jammu

(Registrar/Principal)

Seal

4/10

03-10-2018

Annexure – IX

UNIVERSITY GRANTS COMMISSION BAHADUR SHAH ZAFAR MARG NEW DELHI – 110 002 PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1. Title of the Project: **Unprecedented cascade reactions between ninhydrin and active methylenes : Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation.**

2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR : **Prof. Kamal K. Kapoor, Department of Chemistry, University of Jammu, Jammu.**

3. NAME AND ADDRESS OF THE INSTITUTION : **Department of Chemistry, University of Jammu, Jammu.**

4. UGC APPROVAL LETTER NO. AND DATE : **F.No.43-193/2014(SR) dated 30.10.2015**

5. DATE OF IMPLEMENTATION : **01/07/2015 as per sanction letter dated 30/10/2015. Grant was received in University on 2/12/2015.**

6. TENURE OF THE PROJECT : **3 years**

7. TOTAL GRANT ALLOCATED : **15,57,600 /-**

8. TOTAL GRANT RECEIVED : **Rs. 10,52,100 /-**

9. FINAL EXPENDITURE : **Rs. 5,95,537 /-**

10. TITLE OF THE PROJECT: **Unprecedented cascade reactions between ninhydrin and active methylenes : Synthesis of novel and structurally challenging propellanoids, linearly- and spiro-fused heterocyclic compounds for biological evaluation.**

11. OBJECTIVES OF THE PROJECT :

To explore

1. the chemistry of ninhydrin systematically with a variety of active methylenes having activating groups selected from series: NO_2, CO_2Et, COMe, CN etc. in order to establish mechanistic integrity and structure reactivity relationship for future insight,
2. the transformation of these highly functionalized compounds to novel heterocyclic compounds for 'scaffold hopping' medicinal chemistry,
3. synthesis of novel compounds based on the mechanistic understanding gained from the serendipitous observations obtained,

4. biological significance (antimicrobial and anticancer) of the synthesized compounds by *in vitro* screening,
5. to collaborate with IIIM, Jammu for the utilization of the building blocks in a drug discovery programme,
6. to collaborate with materials scientist to study the new properties of the synthesized heteropolycycles (fused, spiro and propellanoids),
7. to file patents and publish papers on the platform technologies for the synthesis of heteropolycycles (fused, spiro and propellanoids) and other findings emerging out of the proposed project and
8. upgrading the existing laboratory facilities in the Department of Chemistry, University of Jammu, Jammu to perform the sophisticated experiments required to translate the proposed project into reality with proper justification of the financial support, if received.

12. WHETHER OBJECTIVES WERE ACHIEVED : **Yes objectives have been achieved as described in the publications**.

13. ACHIEVEMENTS FROM THE PROJECT : **Four good quality publications in Journals of International repute** [(a) Y. Saini, R. Khajuria, L.K. Rana, G. Hundal, V.K. Gupta, R. Kant and K.K. Kapoor, *Tetrahedron,* **2016**, *72*, 257-263; (b) Y. Saini, R.Khajuria, R. Kaur, S. Kaul, T. Sharma, S. Gupta, V. K. Gupta, R. Kant & K.K. Kapoor, *Synth. Commun.,* **2017**, *72*, 1159-1168; (c) D. Kour, R. Khajuria and K.K. Kapoor, *Tetrahedron Lett.,* **2016**, *57*, 4464-4467; D. Kour, A. Gupta, K.K. Kapoor, V.K. Gupta, Rajnikant, D. Singh and P. Das, *Org. Biomol. Chem.*, **2018**, *16*, 1330-1336].

14. SUMMARY OF THE FINDINGS :

Ninhydrin (Indane-1,2,3-trione), traditionally used for the analysis of amino acids, is known to participate in a number of chemical reactions giving rise to the formation of many structurally functionalized molecules such as aldols, Knoevenagel condensates, phthiocol via 2-hydroxy-2-(1-nitroethyl)-1*H*-indene1,3(2*H*)-dione, *O*-containing heterocycles such as indenofurans, indenopyrans and spiroheterocycles. Fused heterocyclic systems are present in a large variety of natural products and drugs. Indenopyrans are used for the development of many pharmaceutical agents and are known to possess anti-ulcer, anti-depressant and anti-allergenic activities whilst indenofurans constitute part structure of many natural products and are known to exhibit anti-microbial and free radical scavenging properties. Molecules with spirocyclic structures possess activities as hypertensive, analgesic, muscle relaxant, anti-inflammatory and anti-microbial agents. The spiro functionality is also present in phytochemicals such as alkaloids and terpenoids. Further, indene derivatives are also known to be potent therapeutic agents and possess anti-bacterial activities. Also, variety of biologically active natural products are known to posses propellane moiety and these offer tempting and extraordinarily challenging synthetic targets. Fendleridine and 1-acetylaspidoalbidine are used in the treatment of rheumatoid arthritis,

edema, tonsillitis and hypertension, batrachotoxin derived from South American frog *Phyllobates terribilis*, is a steroidal alkaloid skin neurotoxin, milfiensine alkaloid exhibits anticancer activity, hasubanan alkaloids and merrilactone A are used in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Thus, two novel *O*-containing fused heterocycles have been synthesized by ultrasonic-assisted reaction of ninhydrin with ethyl cyanoacetate and diethylmalonate without the use of additives such as catalyst, base etc. Further some interesting indenofurans and 1*H*-indene derivatives have also been synthesized by the reaction of ninhydrin with some other active methylene compounds. Ninhydrin has been employed successfully by various groups in the multi-component reactions for the synthesis of propellanes. Some novel 3-(arylideneamino)-3*a*,8*a*-dihydroxy-1,3,3*a*,8*a* tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and 3-(arylideneamino)-3*a*,8*a* dihydroxy-2-thioxo-1,3,3*a*,8*a*-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-ones have been reported via one-pot catalyst-free reaction of aldehydes, semicarbazide hydrochloride/thiosemicarbazide with ninhydrin. All the synthesized compounds have been screened for anti-microbial activity and some of them were observed to possess broad spectrum anti-bacterial potential as well as significant antagonistic potential against fungal pathogens. A general strategy for the synthesis of novel indenofused heterocyclic motifs through one-pot multicomponent reaction between ninhydrin, malononitrile and various binucleophiles was developed. A versatile method for the preparation of derivatives of Spiro[indene-2,2'-indeno[1,2-*b*]furan]-1,3,4'(8b'*H*)-triones derivatives of quinoxalinones and Indeno[1,2-*b*]pyran-3-carbonitrile derivatives of quinoxalinones with ninhydrin were reported. Owing to the attractive properties of imidazo[1,2-*a*]pyridines, a protocol involving I_2–NH_4OAc promoted one-pot metal-free synthesis of diversely substituted imidazo[1,2-*a*]pyridines from 2-aminopyridine and aryl methyl ketones was established. Also, an efficient, metal-free regioselective synthesis of 2-aroyl-3-arylimidazo [1,2-*a*]pyridines from 1,3-diaryl-prop-2-en-1-ones and 2-aminopyridine was carried out. The iodine–NH4OAc promoted reaction offers a novel route in the synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines. This protocol offers significant flexibility in accessing medicinally important 2-aroyl-3-arylimidazo[1,2-*a*]pyridines with various substitution patterns.

15. CONTRIBUTION TO THE SOCIETY : **Newer applications of ninhydrin in organic syntheses for variety of diverse scaffolds. These findings have added value to the chemistry literature to carry out reactions without the use of toxic metallic catalysts.**

16. WHETHER ANY PH.D. ENROLLED/PRODUCED OUT OF THE PROJECT : **Yes.**

17. NO. OF PUBLICATIONS OUT OF THE PROJECT : **4 publications (enclosed herein).**

Dr. Kamal K. Kapoor
Principal Investigator
UGC Project No. MRP-[illegible]/CHEM-2013-21745
Department of Chemistry
University of Jammu

(PRINCIPAL INVESTIGATOR)

Registrar
University of Jammu

(REGISTRAR/PRINCIPAL)

(Seal)

17/10

10-10-18

(CO-INVESTIGATOR)

UNIVERSITY OF JAMMU

No: Grants/2018/2168
Dated: 4/1/2019

TO WHOM SO EVER IT MAY CONCERN

It is certified that the University of Jammu is in receipt of all the UGC Projects related funding in a common current account having account no-0345010100000001, IFSC Code-JAKAOCANAAL, MICR code-180051018 and branch code-0345, operated by the Registrar, University of Jammu and maintained by the J&K Bank Ltd, New University Campus Branch, Jammu.

Since the said account is current in nature and no interest is earned on the same, however, the University of Jammu is going to implement new system of accounting wherein it shall be possible to calculate interest on individual grants, for further necessary action as required. In this regard, a separate interest bearing account has been created which will become operational in the next financial year.

REGISTRAR

Mandate form for the institutions Registered/Mapped under PFMS

ELECTRONIC CLEARING SERVICE (CREDIT CLEARING) / REAL TIME GROSS SETTLEMENT (RTGS) FACILITY FOR RECEIVING PAYMENT

A. DETAILS OF ACCOUNT HOLDER-

ACCOUNT HOLDER (Registrar/Director)	The Registrar, University of Jammu, Jammu
COMPLETE CONTACT ADDRESS	1st Floor, New Administration Block, Babasahed Ambedkar Road, New University Campus, Jammu Taw, Jammu 180 006
Telephone no / email	0191 – 2431365/2430935

B. BANK ACOUNT DETAILS-

Bank name	The Jammu & Kashmir Bank Ltd.
Branch name with complete address, telephone number and email	J & K Bank, New University Campus Branch, Jammu 180 006 0191 – 2458663/canal@jkbmail.com
Whether branch is computerized?	YES
Whether the branch is RTGS enabled? If yes, provide IFSC code of branch	YES IFSC Code – JAKA0CANAAL
Is branch also NEFT enabled?	YES
Type of bank A/c (SB/current/cc)	SAVING
Complete bank A/c number (Latest)	0345040160000001
MICR Code of the Bank	180051018
Branch Code	0345
Unique Code of the PFMS	J

I hereby declare that the particulars given above are correct and complete. If the transaction is delayed, or not effected at all for reasons of incomplete or incorrect information, I would not hold the user institution responsible. I have read the option invitation letter and agree to discharge responsibility expected of me as a participant under the Scheme.

The above institution, account number and bank detail are registered/ mapped under Public Finance Management System (PFMS).

.....
(Signature)
Registrar
University of Jammu

Place: Jammu
Date: 01/08/2018

Certified that the particulars furnished above are correct as per our records

(Bank Stamp)
Date: 01/08/2018

(Signature of authorized official from the Bank)

UNIVERSITY OF JAMMU

No: Grants/2018/1993-95
Dated: 06/12/18

The Under Secretary (FD-III),
University Grants Commission,
Bahadur Shah Zafar Marg,
New Delhi - 110 002.

Sub:- **Refund of unspent balance of UGC MRP sanctioned vide F.No.43-193/2014 (SR) dated 30, October,2015.**

Sir/Madam,

Kindly find enclosed herewith copy of Statement of Expenditure and Utilization Certificate of project entitled **"Unprecedented cascade.....spiro-fused heterocy"** sanctioned in favour of Dr.Kamal K Kapoor, Department of Chemistry, University of Jammu vide sanction No. **F. No. 43-193/2014 (SR) dated 30, October,2015** along-with refund of unspent balance of Rs. 4,56,563/- vide instrument No. JAKAR201812035337500430 dated 03/12/2018 through J & K Bank Ltd., New University Campus Branch, University of Jammu for further necessary action and consideration.

Kindly acknowledge the receipt of the same.

Thanking you,

Yours faithfully,

Sumitra Sharma
4/12/18.

Assistant Registrar (Grants)

Copy to: -

1. Dr. Kamal K Kapoor, Department of Chemistry, University of Jammu, Jammu for information
2. Sr. P.A. to Joint Registrar (F).

6/12/18

Tetrahedron 72 (2016) 257–263

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Unprecedented reaction of ninhydrin with ethyl cyanoacetate and diethyl malonate on ultrasonic irradiation

Yeshwinder Saini [a], Rajni Khajuria [a], Love Karan Rana [b], Geeta Hundal [b], Vivek K. Gupta [c], Rajni Kant [c], Kamal K. Kapoor [a,*]

[a] Department of Chemistry, University of Jammu, Jammu 180 006, India
[b] X-ray Crystallography Group, Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India
[c] X-ray Crystallography Group, Department of Physics & Electronics, University of Jammu, Jammu 180 006, India

ARTICLE INFO

Article history:
Received 24 June 2015
Received in revised form 17 October 2015
Accepted 12 November 2015
Available online 2 December 2015

Keywords:
Indenopyrans
Indenofurans
Spiroindenofuran
1*H*- indene
Ultrasonication

ABSTRACT

Ultrasonic-assisted, catalyst-free reactions of ninhydrin with ethyl cyanoacetate and diethyl malonate led to the unprecedented formation of an indenopyran and a spiroindenofuran *viz.* diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** and diethyl 3a′,8b′-dihydroxy-1,3,4′-trioxo-1,3,3a′,4′-tetrahydrospiro[indene-2,2′-indeno[1,2-b]furan]-3′,3′(8b′*H*)-dicarboxylate **3**, respectively. In addition to these unprecedented results, reactions of ninhydrin with dimedone, ethyl acetoacetate and ethyl nitroacetate yielded 4b,9b-dihydroxy-7,7-dimethyl-7,8-dihydro-4b*H*-indeno[1,2-*b*]benzofuran-9,10(6*H*,9b*H*)-dione **5**, ethyl 3a,8b-dihydroxy-2-methyl-4-oxo-4,8b-dihydro-3a*H*-indeno[1,2-*b*]furan-3-carboxylate **6** and 2-hydroxy-2-(nitromethyl)-1*H*-indene-1,3(2*H*)-dione **7**, respectively. The structures of **1**, **3**, **5**, **6** and **7** were determined by X-ray crystallography and attempts have been made to propose the mechanism of their formation.

1. Introduction

Ninhydrin (Indane-1,2,3-trione), traditionally used for the analysis of amino acids,[1] is known to participate in a number of chemical reactions giving rise to the formation of many structurally functionalized molecules such as aldols,[2] Knoevenagel condensates,[2] phthiocol via 2-hydroxy-2-(1-nitroethyl)-1*H*-indene-1,3(2*H*)-dione,[3] O-containing heterocycles such as indenofurans,[2] indenopyrans[4] and spiroheterocycles.[5] Fused heterocyclic systems are present in a large variety of natural products and drugs.[6] Indenopyrans are used for the development of many pharmaceutical agents[7] and are known to possess *anti*-ulcer, *anti*-depressant and *anti*-allergenic activities[8] whilst indenofurans constitute part-structure of many natural products and are known to exhibit *anti*-microbial and free radical scavenging properties[9] (see Figs. 1 and 2). Molecules with spirocyclic structures possess activities as hypertensive, analgesic, muscle relaxtant, *anti*-inflammatory and *anti*-microbial agents.[10] The spiro functionality is also present in phytochemicals such as alkaloids and terpenoids.[11] Further, indene derivatives are also known to be potent therapeutic agents and possess *anti*-bacterial activities.[12]

2. Genesis

Ninhydrin on reaction with 1 equiv of active methylene yields aldols **A** and Knoevenagel condensates **B**. Some aldols are further known to produce intramolecular cyclisation products such as indenofurans **C** (Scheme 1).[2,13] These aldols and Knoevenagel condensates are highly functionalized and are capable of undergoing further reactions with active methylenes and reactive carbonyl compounds (e.g., ninhydrin), respectively. Knoevenagel product **B**, in particular has attracted our attention since the nature of EWG_1 and EWG_2 can influence the attack of second active methylene molecule. This may lead to the formation of Michael products **D** and **E**. Further intramolecular reactions of **D** and **E** may lead to respective cyclic products. We wished to probe into the reaction of aldols and Knoevenagel condensates with active methylene compounds in a quest to obtain newer heterocyclic products (path **a** and **b**) (Scheme 2). Aldol **A** may capture another molecule of ninhydrin leading to the formation of spiroindenofuran derivatives of type **F** (path **c**) (Scheme 2).

* Corresponding author. E-mail address: k2kapoor@yahoo.com (K.K. Kapoor).

http://dx.doi.org/10.1016/j.tet.2015.11.022
0040-4020/

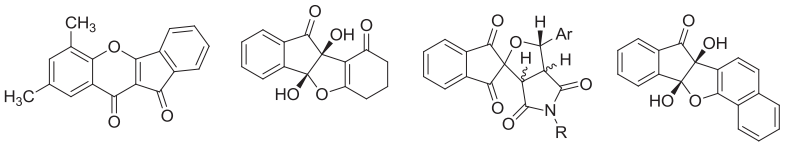


Fig. 1. Some biologically important indenopyran and indenofuran derivatives.[7d,9b–d,10e]

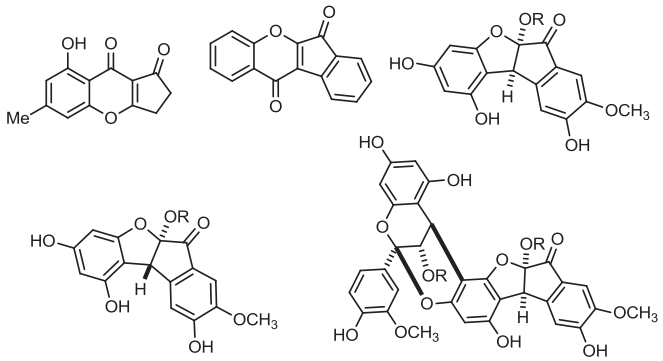
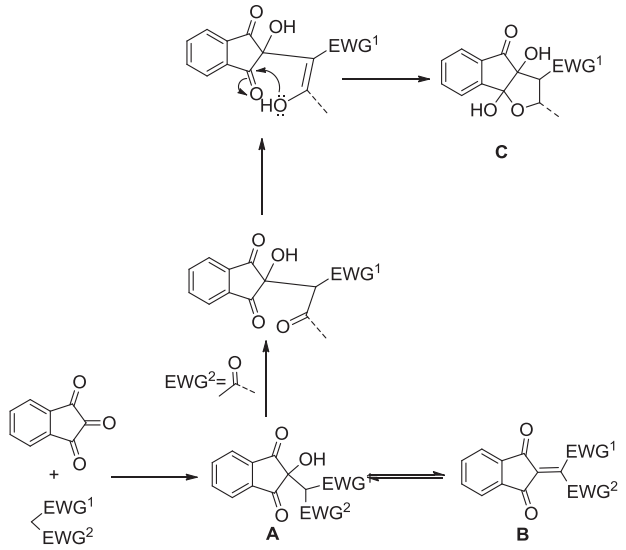


Fig. 2. Some natural products containing indenopyran[7d] and indenofuran substructures.[9a]



Scheme 1. Products of the reaction of ninhydrin with 1 equiv of active methylene.

3. Results and discussion

When ninhydrin is reacted with ethyl cyanoacetate (ECA) in water, reported[2] aldol product of type **A** separates out as white solid. We thought of using ethanol instead of water with a hope that the aldol product does not precipitate out and undergoes further reaction as proposed in genesis leading to the formation of newer products. With this perspective in mind, 1:1 mixture of ninhydrin and ethyl cyanoacetate was stirred at room temperature using ethanol as solvent and the progress of the reaction was monitored using TLC. After 7 h of stirring, formation of two new products was observed. The two products were isolated as crystalline solids and characterized, respectively as diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** (32%) and diethyl 2,2′-(1,3-dioxo-2,3-dihydro-1*H*-indene-2,2-diyl)bis(2-cyanoacetate) **2** (15%). Further corroboration of structures **1** and **2** was arrived at by X-ray crystallographic studies (Fig. 3). To improve the yields, attempts such as (i) performing above reaction in refluxing ethanol, microwave irradiation, ultrasonic-irradiation **(entries 1–3)** and (ii) replacing ethanol with other organic solvents **(entries 4–11)** were made (Table 1).

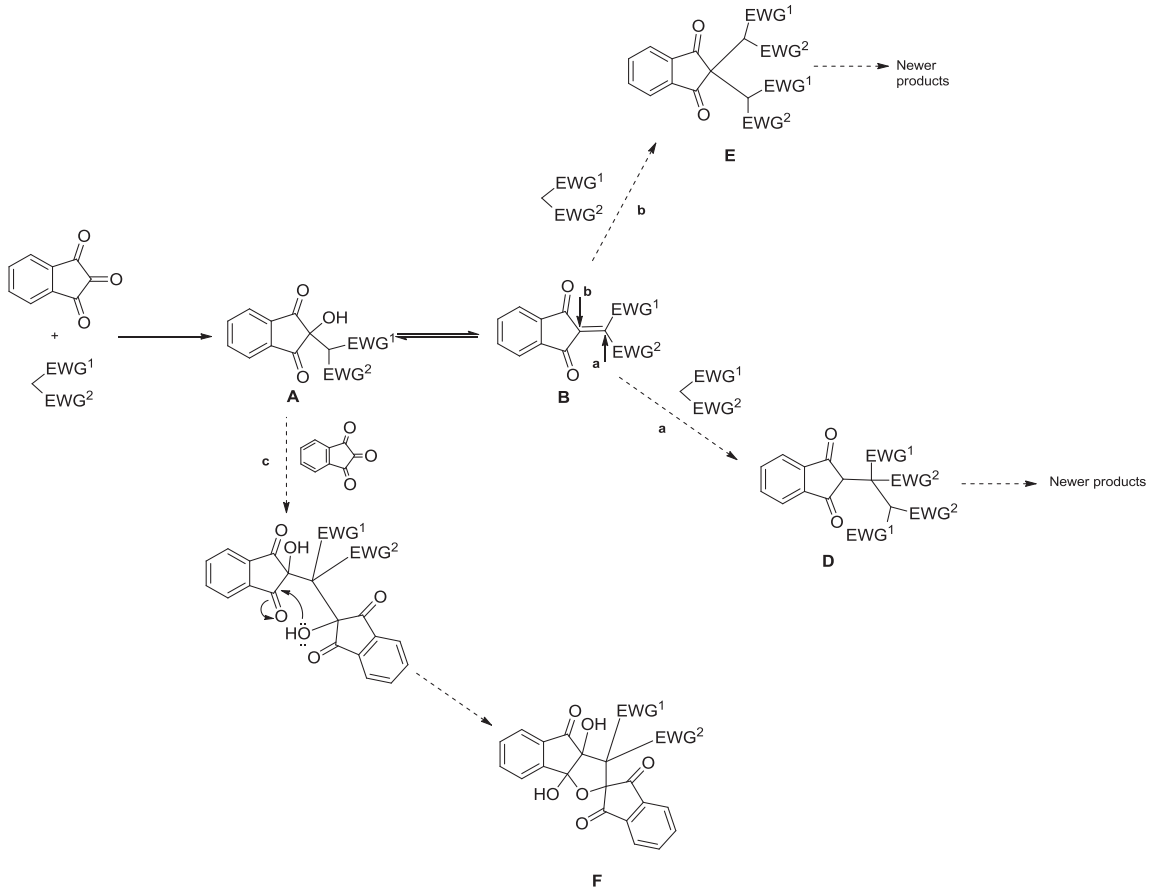
It was found that use of ethanol as solvent on ultrasonic-irradiation gave best results (**entry 3**). Slight improvement in yields of products **1** (from 54% to 61%) and **2** (from 20% to 24%) was observed in a reaction of ninhydrin with 2 equiv of ethyl cyanoacetate (Scheme 3).

The plausible mechanism for the formation of diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-*b*]pyran-3,4-dicarboxylate **1** and diethyl 2,2′-(1,3-dioxo-2,3-dihydro-1*H*-indene-2,2-diyl)bis(2-cyanoacetate) **2** is shown in Scheme 4.

Ultrasonication of ethanolic solution of 1:1 mixture of ninhydrin and diethyl malonate (DEM) yielded diethyl 3a′,8b′-dihydroxy-1,3,4′-trioxo-1,3,3a′,4′-tetrahydrospiro[indene-2,2′-indeno[1,2-b]furan]-3′,3′(8b′*H*)-dicarboxylate **3** and previously reported[2] aldol product diethyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)malonate **4** in 53 and 24% yields, respectively. However, when the reaction was carried out with 2:1 mixture of ninhydrin and diethyl malonate, improvement in yield of the spiro product **3** (64%) was noticed (Scheme 5). Mechanistically, this is in resonance with that proposed by Holzer et al. for the reaction of ninhydrin with methyl(di)azines having methyl group in α-position to the ring nitrogen atom.[5c]

Plausible mechanism for the formation of **3** is shown in Scheme 6. Diethyl malonate captures two molecules of ninhydrin in a stepwise manner to produce **G**, which cyclizes intramolecularly to produce **3.**

In addition to above unprecedented results the reaction of ninhydrin with dimedone, ethyl acetoacetate (EAA) and ethyl nitroacetate (ENA) gave expected products.The reaction of ninhydrin with dimedone has been reported[13] to yield the aldol product of type **A**. To our delight similar reaction on ultrasonic-irradiation in ethanol led to the formation of the cyclized indenofuran derivative 4b,9b-dihydroxy-7,7-dimethyl-7,8-dihydro-4b*H*-indeno[1,2-*b*]benzofuran-9,10(6*H*,9b*H*)-dione **5** in 96% yield. A product resembling with **5** has been reported by Mehdi et al.[9b] by the reaction of ninhydrin with cyclohexane-1,3-dione on refluxing using acetic acid as solvent. Being eco-friendly and convenient, our method is advantageous over this reported method. The reaction of ninhydrin with ethyl acetoacetate (EAA) yielded reported product[2,12] ethyl 3a,8b-dihydroxy-2-methyl-4-oxo-4,8b-dihydro-3a*H*- indeno[1,2-*b*]furan-3-carboxylate **6** in 95% yield. Ethyl nitroacetate (ENA) upon reaction with ninhydrin under similar conditions yielded 1*H*-indene derivative 2-hydroxy-2-(nitromethyl)-1*H*-indene-1,3(2*H*)-dione **7** (78%) after de-ethyldecarboxylation of the aldol product (Scheme 7, Fig. 3).

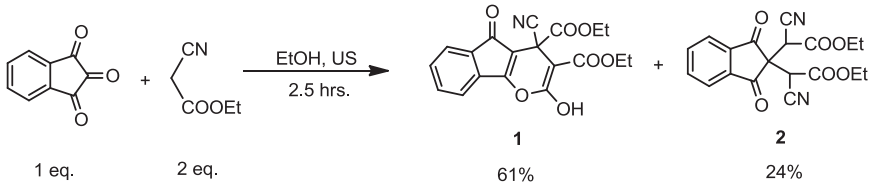


Scheme 2. Possible products expected from aldol and Knoevenagel condensates.

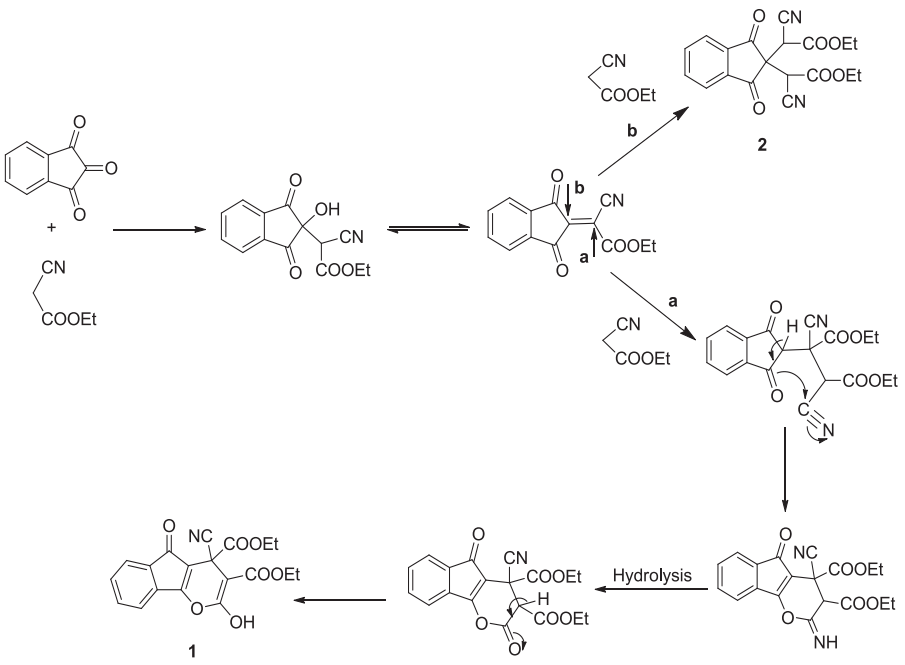
Table 1
Optimization of the reaction conditions

Entry	Solvent/mode	Time (hrs)	Yield (%)	
			1	2
1	EtOH/Reflux	5	44	16
2	EtOH/Microwave irradiation	3	45	18
3	**EtOH/Ultrasound**	**2.5**	**54**	**20**
4	MeOH/Ultrasound	2.5	46	20
5	^{i}PrOH/Ultrasound	2.5	43	19
6	CH_3CN/Ultrasound	2.5	40	17
7	THF/Ultrasound	2.5	37	14
8	Dioxane/Ultrasound	2.5	37	15
9	Acetone/Ultrasound	2.5	36	14
10	$CHCl_3$/Ultrasound	2.5	30	12
11	1,2-DCE/Ultrasound	2.5	31	15

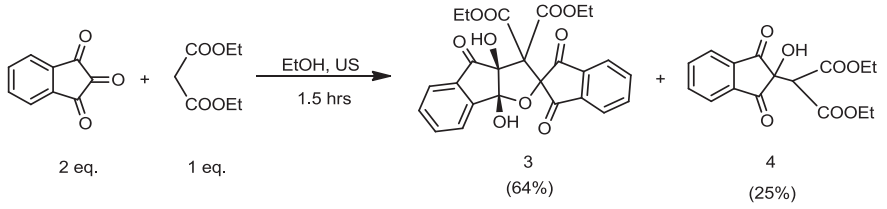
Bold entry emphasize and highlight the reaction condition which gave the best results.



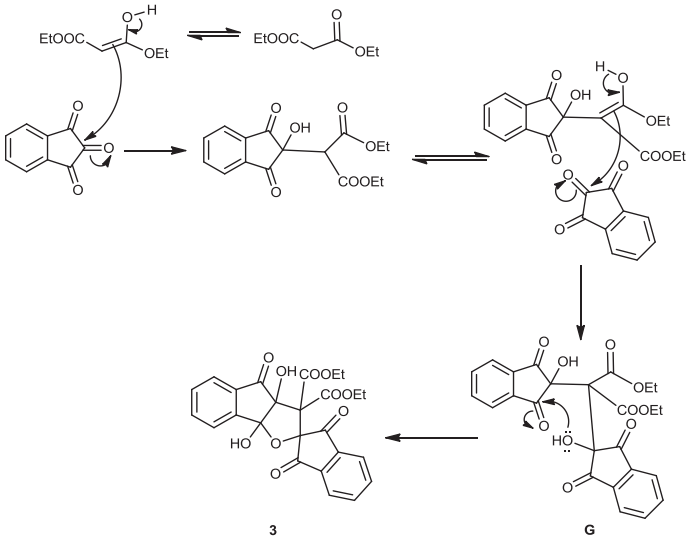
Scheme 3. Ultrasonic-assisted reaction of ninhydrin with ethyl cyanoacetate.



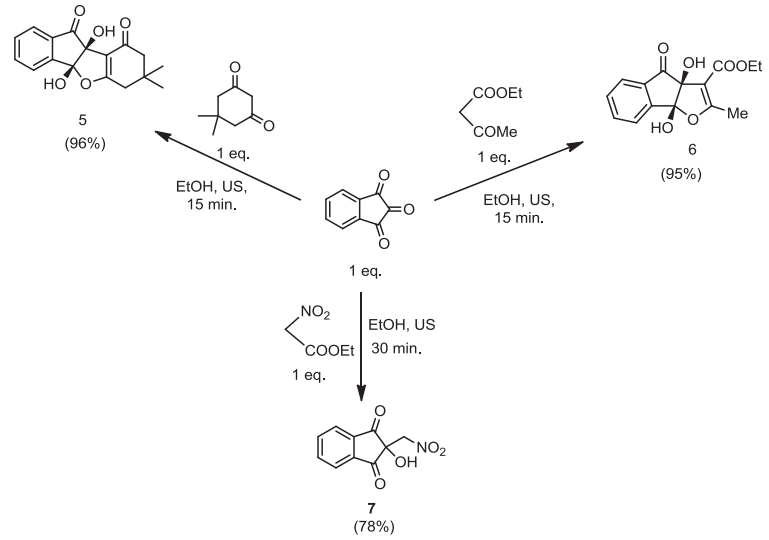
Scheme 4. Plausible mechanism for the formation of **1** and **2**.



Scheme 5. Ultrasonic-assisted reaction between ninhydrin and diethyl malonate.



Scheme 6. Proposed mechanism for the formation of **3**.



Scheme 7. Ultrasonic-assisted reaction of ninhydrin with dimedone, ethyl acetoacetate and ethyl nitroacetate.

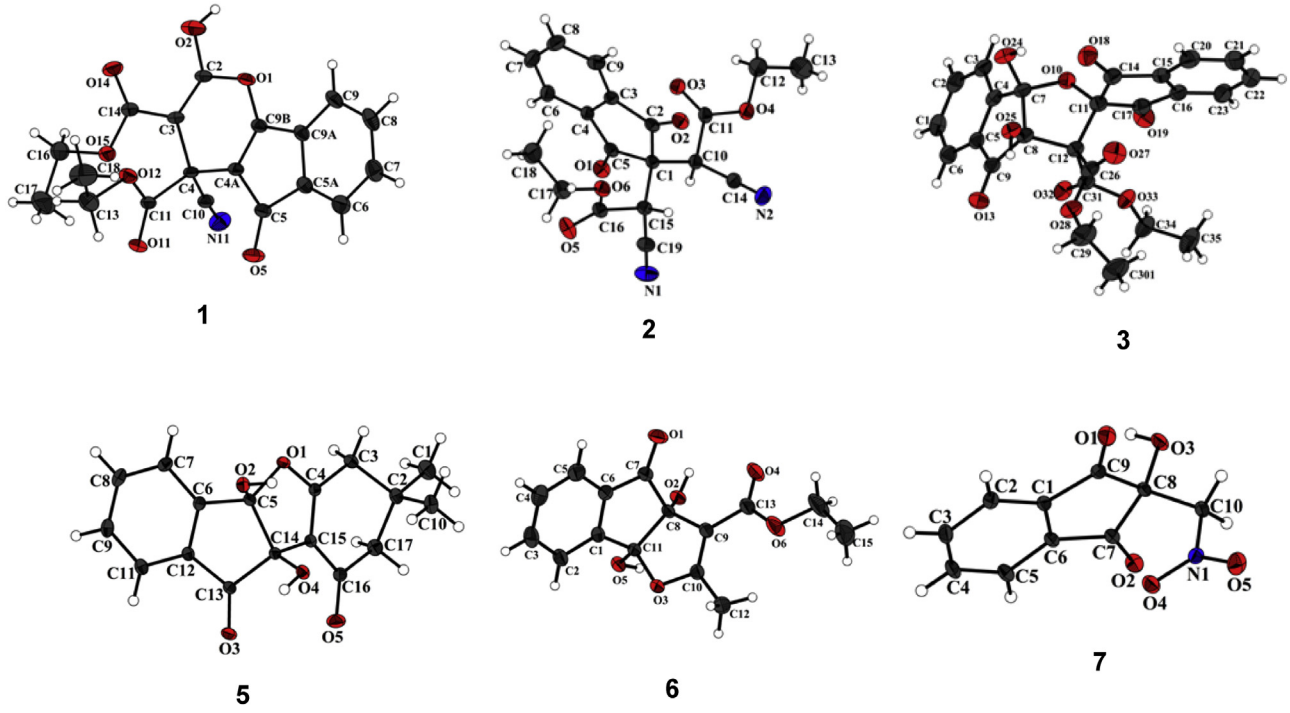


Fig. 3. X-ray crystal structures of **1**, **2**, **3**, **5**, **6** and **7**.

The reaction of ninhydrin with acetylacetone, malononitrile and malonic acid gave 3-acetyl-3a,8b-dihydroxy-2-methyl-3a*H*-indeno [1,2-*b*]furan-4(8b*H*)-one, 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene) malononitrile and 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1*H*-inden-2-yl)acetic acid in 94%, 82% and 90% yields, respectively akin to those reported by Chakarbarty et al.[2]

4. Conclusions

Two novel O-containing fused heterocycles (**1** and **3)** have been synthesized by ultrasonic-assisted reaction of ninhydrin with ethyl cyanoacetate and diethylmalonate without the use of additives such as catalyst, base etc. Plausible mechanisms are proposed to explain the formation of new compounds. Further some interesting indenofurans (**5** and **6**) and 1*H*-indene derivatives (**2**, **4** and **7**) have also been synthesized by the reaction of ninhydrin with some other active methylene compounds.

5. Experimental section

5.1. General procedures

All the experiments were performed in an oven dried glass apparatus. All the commercially available reagents were purchased from *Aldrich* and were used without further purification. Ultrasonication was performed on 2510 Branson Ultrasonicator.

Microwave irradiation (MWI) was done on CEM Discover Microwave. X-ray data[14] were collected on a Bruker Kappa Apex-II diffractometer at RT with Mo-Kα radiation (λ=0.71073 Å) at Department of Chemistry, Centre for Advanced Studies, Guru Nanak Dev University, Amritsar and *X′calibur* CCD area-detector diffractometer equipped with graphite monochromated MoKα radiation (λ=0.71073 Å), Department of Physics and Electronics, University of Jammu, Jammu. Melting points (°C) were measured in open glass capillaries using Perfit melting point apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography (TLC) using silica gel pre-coated aluminium sheets (60 F254, Merck). Visualization of spots was effected by exposure to ultraviolet light (UV) at 365 nm and 254 nm, iodine vapours and 2% 2,4-dinitrophenylhydrazine in methanol containing few drops of H_2SO_4 and draggendroff reagent. Recrystallization was achieved with ethanol. IR spectra (ν, cm^{-1}) were recorded on Perkin–Elmer FTIR spectrophotometer using KBr discs. ^1H and ^{13}C NMR were recorded on Bruker AC-400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from TMS. *J* values are given in Hertz (Hz). The abbreviations s, d, dd, t, q and m in ^1H NMR spectra refer to singlet, doublet, doublet of doublet, triplet, quartet and multiplet, respectively. For the HRMS measurement, Q-TOF was used. Commercial grade solvents were dried as per established procedure before use.[15] Solvents were removed using Heidolph rotary evaporator. Common abbreviations are used throughout, mp for melting point, US for ultrasonication, ECA for ethyl cyanoacetate, DEM for diethyl malonate, EAA for ethyl acetoacetate, ENA for ethyl nitroacetate.

5.2. General procedure for the synthesis

A mixture of ninhydrin(0.36 g, 2 mmol) and active methylene (4 mmol in case of ECA, 1 mmol in case of DEM, 2 mmol in case of dimedone, EAA and ENA) was ultrasonicated in ethanol (10 ml) till the completion of the reaction (TLC). Solvent was concentrated in vacuo and the resultant was dissolved in ethyl acetate (30 ml), washed with water (5×10 ml), brine (2×10 ml) and dried over anhydrous Na_2SO_4. Ethyl acetate was concentrated in vacuo and the product obtained was purified by column chromatography using a gradient of ethyl acetate and petroleum ether as eluents, followed by recrystallization with ethanol or chloroform.

*5.2.1. Diethyl 4-cyano-2-hydroxy-5-oxo-4,5-dihydroindeno[1,2-b]pyran-3,4-dicarboxylate (**1**).* Yellow crystalline solid (0.45 g, 61% yield); mp 220–222 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J*=6.7 Hz, 1H), 7.43 (m, 2H), 7.28 (d, *J*=6.8 Hz, 1H), 4.42–4.20 (m, 4H), 1.39 (t, *J*=7.1 Hz, 3H), 1.32 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.21, 167.40, 166.99, 166.77, 159.48, 134.37, 133.02, 131.85, 131.19, 123.04, 119.47, 117.06, 104.29, 75.63, 63.70, 61.26, 40.42, 13.96; IR (KBr) ν_{max}/cm^{-1}: 3397.81, 3296.16, 1747.34, 1695; HRMS (ESI): calcd for $C_{19}H_{15}NO_7$ $[M+H]^+$, 370.0922; found: 370.0904.

*5.2.2. Diethyl 2,2′-(1,3-dioxo-2,3-dihydro-1H-indene-2,2-diyl)bis(2-cyanoacetate) (**2**).* White crystalline solid (0.18 g, 24% yield); mp 125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12–8.04 (m, 2H), 8.00–7.92 (m, 2H), 4.68 (s, 1H), 4.62 (s, 1H), 4.26 (q, *J*=7.1 Hz, 2H), 4.01 (dd, *J*=7.1, 4.6 Hz, 2H), 1.30 (t, *J*=7.1 Hz, 3H), 1.13 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.45, 193.36, 162.54, 162.07, 141.92, 141.37, 137.08, 136.57, 124.21, 123.75, 112.16, 111.78, 64.41, 53.71, 51.89, 41.15, 39.87, 13.80, 13.52; **IR** (KBr) ν_{max}/cm^{-1}: 1746.77, 1716.84, 3453.18; HRMS (ESI): calcd for $C_{19}H_{16}N_2O_6$ $[M+H]^+$, 369.1081; found: 369.1071.

*5.2.3. Diethyl 3a′,8b′-dihydroxy-1,3,4′-trioxo-1,3,3a′,4′-tetrahydrospiro[indene-2,2′-indeno[1,2-b]furan]-3′,3′(8b′H)-dicarboxylate (**3**).* White crystalline solid (0.3 g, 64% yield); mp 203 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10–8.07 (m, 1H), 7.96–7.91 (m, 4H), 7.83 (dd, *J*=6.7, 0.8 Hz, 1H), 7.77 (dd, *J*=7.4, 6.3 Hz, 1H), 7.65 (dd, *J*=7.2, 6.5 Hz, 1H), 6.14 (s, 1H), 4.32 (dt, *J*=10.7, 5.3 Hz, 2H), 4.22 (dd, *J*=11.9, 7.2 Hz, 2H), 3.77 (s, 1H), 1.27 (t, *J*=7.2 Hz, 3H), 1.18 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.99, 193.43, 166.40, 165.30, 147.12, 141.07, 136.90, 136.77, 136.30, 135.20, 131.23, 124.43, 124.03, 123.61, 110.27, 84.08, 63.51, 62.90, 13.64, 13.51; IR (KBr) ν_{max}/cm^{-1}: 3440.85, 1731.82, 1716.05; HRMS (ESI): calcd for $C_{25}H_{20}O_{10}$ $[M+H]^+$, 481.1129; found: 481.1127.

*5.2.4. Diethyl 2-(2-hydroxy-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)malonate (**4**).* Yellow gummy material (0.16 g, 25% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09–7.98 (m, 2H), 7.94–7.86 (m, 2H), 4.31–4.15 (m, 4H), 4.07–4.03 (m, 1H), 1.33–1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.09, 167.34, 141.02, 136.30, 124.25, 73.40, 62.67, 53.32, 13.73; IR (KBr) ν_{max}/cm^{-1}: 1746.69, 1716.80; HRMS (ESI): calcd for $C_{16}H_{16}O_7$ $[M+H]^+$, 321.0969; found: 321.0958.

*5.2.5. 4b,9b-Dihydroxy-7,7-dimethyl-7,8-dihydro-4bH-indeno[1,2-b]benzofuran-9,10(6H,9bH)-dione (**5**).* White crystalline solid (0.57 g, 96% yield); mp 210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.85 (m, 2H), 7.75 (dd, *J*=5.5, 3.0 Hz, 2H), 3.51 (s, 1H, OH), 2.28 (s, 4H), 2.19 (s, 1H, OH), 1.05 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.52, 192.14, 175.99, 147.28, 136.65, 134.66, 131.88, 125.36, 123.50, 112.98, 111.80, 83.05, 51.60, 37.67, 33.45, 28.70, 27.86; IR (KBr) ν_{max}/cm^{-1}: 3436.60, 1725.23; HRMS (ESI): calcd for $C_{17}H_{16}O_5$ $[M+H]^+$, 301.1071; found: 301.1070.

*5.2.6. Ethyl 3a,8b-dihydroxy-2-methyl-4-oxo-4,8b-dihydro-3aH-indeno[1,2-b]furan-3-carboxylate (**6**).* White crystalline solid (0.55 g, 95% yield): mp 96 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.8 Hz, 1H), 7.84 (dd, *J*=15.8, 7.8 Hz, 2H), 7.64 (t, *J*=7.5 Hz, 1H), 4.90 (s, 1H), 4.58 (s, 1H), 4.33–4.23 (m, 2H), 2.25 (s, 3H), 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.21, 170.50, 164.39, 146.73, 136.50, 134.38, 131.43, 124.58, 124.12, 108.48, 103.76, 83.59, 60.43, 15.03, 14.36; IR (KBr) ν_{max}/cm^{-1}: 3435.69, 1729.04; HRMS (ESI): calcd for $C_{15}H_{14}O_6$ $[M+H]^+$, 291.0863; found: 291.0839.

*5.2.7. 2-Hydroxy-2-(nitromethyl)-1H-indene-1,3(2H)-dione (**7**).* White crystalline solid (0.34 g, 78% yield): mp 160 °C; ^1H NMR (400 MHz, MeOD) δ 8.15–8.02 (m, 4H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, MeOD) δ 196.49, 140.75, 136.60, 123.74, 73.93, 71.23; IR (KBr) ν_{max}/cm^{-1}: 3326.67, 1702.69; HRMS (ESI): calcd for $C_{10}H_7NO_5$ $[M+H]^+$, 222.0397; found: 222.0378.

Acknowledgements

Authors are grateful to University Grants Commission, New Delhi (Project No. MRP-MAJOR-CHEM-2013-21745) for funding and the Department of Science and Technology, New Delhi for NMR facility under PURSE. RK is also thankful to University Grants Commission, New Delhi for Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.11.022.

References and notes

1. Joullie, M. M.; Thompson, T. R.; Nemeroff, N. H. *Tetrahedron* **1991**, *47*, 8791.
2. Chakrabarty, M.; Mukherji, A.; Arima, S.; Harigaya, Y.; Pilet, G. *Montash Chem.* **2009**, *140*, 189–197.
3. Lukats, B.; Clauder, O. *Acta Chim. Acad. Sci. Hung* **1972**, *71*, 93–100.
4. (a) Boulos, L. S. *Heteroat. Chem.* **1997**, *8*, 253–257; (b) Khurana, J. M.; Yadav, S. *Aust. J. Chem.* **2012**, *65*, 314–319.

5. (a) Venkov, A. P.; Lukanov, L. K. *Synth. Commun.* **1996**, *26*, 755–762; (b) Lehmier, H.-J.; Nieger, M.; Breitmaier, E. *Synthesis* **1996**, *1*, 105–110; (c) Heinisch, G.; Holzer, W.; Mereiter, K.; Strobl, B.; Zheng, C. *Heterocycles* **1996**, *43*, 1665–1679; (d) Schank, V. K.; Lieder, R.; Lick, C.; Glock, R. *Helv. Chem. Acta* **2004**, *87*, 869–924; (e) Hasaninejad, A.; Golzar, N.; Shekouhy, M.; Zare, A. *Helv. Chim. Acta* **2011**, *94*, 2289–2294.
6. Jin, J.; Luo, Y.; Zhou, C.; Chen, X.; Wen, Q.; Lu, P.; Wang, Y. *J. Org. Chem.* **2012**, *77*, 11368–11371.
7. (a) Karnik, A. V.; Kulkarni, A. M.; Malviya, N. J.; Mourya, B. R.; Jadhav, B. L. *Eur. J. Med. Chem.* **2008**, *43*, 2615–2617; (b) Jin, T. S.; Zhang, J. –S.; Liu, L. –B.; Wang, A.-Q.; Li, T.-S. *Synth. Commun.* **2006**, *36*, 2009–2015; (c) Costi, M. P.; Tondi, D.; Pecorari, P.; Rinaldi, M.; Celentano, G.; Ghelli, S.; Antolini, L.; Barlocco, D. *J. Heterocycl. Chem.* **1999**, *36*, 1043–1048; (d) Thasana, N.; Ruchirawat, S. *Tetrahedron Lett.* **2002**, *43*, 4515–4517; (e) Wang, H.-J.; Gloer, J. B. *Tetrahedron Lett.* **1995**, *36*, 5847–5850; (f) Lin, L. –J.; Topcu, G.; Lotter, H.; Ruangrungsi, N.; Wagner, H.; Pezzuto, J. M.; Cordell, G. A. *Phytochemistry* **1992**, *31*, 4333–4335.
8. (a) Pelz, K.; Dobson, T. A. US Patent 3904617 1975, *Chem. Abstr.* **2008**, *84*, 164794; (b) Jirkovsky, I.; Humber, L. G.; Noureldin, R. *Eur. J. Med. Chem.* **1976**, *11*, 571; (c) Goerlitzer, K.; Dehne, A.; Engler, E. *Arch. Pharm.* **1983**, *316*, 264; (d) Khaligh, N. G. *Tetrahedron Lett.* **2012**, *53*, 1637–1640.
9. (a) Azuma, T.; Tanaka, Y.; Kikuzaki, H. *Phytochemistry* **2008**, *69*, 2743–2748; (b) Mehdi, S. H.; Hashim, R.; Ghalib, R. M.; da Silva, M. F. G. C.; Sulaiman, O.; Rahman, S. Z.; Murugaiyah, V.; Marimuthu, M. M. *J. Mol. Str.* **2011**, *1006*, 318–323; (c) Prabhakar, K. R.; Veerapuri, V. P.; Bansal, P.; Vipan, K. P.; Reddy, K. M.; Barik, A.; Reddy, B. K. D.; Reddanna, P.; Priyadarsini, K. I.; Unnikrishnan, M. K. *Bioorg. Med. Chem.* **2006**, *14*, 7113–7120; (d) Prabhakar, K. R.; Veerapuri, V. P.; Bansal, P.; Vipan, K. P.; Reddy, K. M.; Barik, A.; Reddy, B. K. D.; Reddanna, P.; Priyadarsini, K. I.; Unnikrishnan, M. K. *Bioorg. Med. Chem.* **2013**, *21*, 2177.
10. (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164; (b) Gadwood, R. C.; Kamdar, B. V.; Dubray, L. A. C.; Wolfe, M. L.; Smith, M. P.; Watt, W.; Mizsak, S. A.; Groppi, V. E. *J. Med. Chem.* **1993**, *36*, 1480; (c) Bourdonnec, B. L.; Windh, R. T.; Leister, L. K.; Zhou, Q. J.; Ajello, C. W.; Gu, M.; Chu, G. –H.; Tuthill, P. A.; Barker, W. M.; Koblish, M.; Graczyk, D. D. T. M.; Belanger, S.; Cassel, J. A.; Freschenko, M. S.; Brogdon, B. L.; Smith, S. A.; Derelanko, M. J.; Kutz, S.; Little, P. J.; DeHaven, R. N.; DeHaven-Hudkins, D. L.; Dolle, R. E. *J. Med. Chem.* **2009**, *52*, 5685; (d) Finn, J.; Wang, X. Y.; Yu, Z. G.; Hill, J.; Keith, D.; Gallant, P.; Wendler, P. *Chem. Abstr.* **2000**, *132*, 251137; (e) Lu, C. –D.; Chen, Z. –Y.; Liu, H.; Hu, W. –H.; Mi, A. –Q.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 4856–4859.
11. Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779.
12. (a) Baut, G. L.; Sparfel, L.; Creuzet, M. H.; Feniou, C.; Ponta, H.; Prat, G. *Chem. Abstr.* **1986**, *105*, 60434; (b) El, D.; Nabaweya, S. *Acta Pharm.* **1999**, *49*, 119.
13. (a) Peet, N. P.; Huber, E. W. *J. Heterocycl. Chem.* **1995**, *32*, 33; (b) Kundu, S. K.; Patra, A.; Pramanik, A. *Ind. J. Chem.* **2004**, *43B*, 604–611.
14. Crystal data of product **1**: $C_{19}H_{15}N_1O_7$, Mol. wt 369.32, Wavelength=0.71073 Å, Monoclinic, $P2_1/n$, a=9.1471(4) Å, b=16.06905(5) Å, c=12.5306(5) Å, β=92.765(4)°, V=1839.66(12) Å^3, Z=4, D_{calcd}=1.333 Mg/m^3, $R1$=0.0710, w$R2$=0.1659(for observed data), $R1$=0.0961, w$R2$=0.1800 for all data. CCDC No. **940836**. Crystal data of product **2**: $C_{19}H_{16}N_2O_6$, Mol. wt 368.34, Wavelength=0.71073 Å, Triclinic, P-1, a=8.1354(10) Å, b=10.1871(11) Å, c=11.9485(14) Å, α=70.079(3)°, β=75.632(5)°, γ=77.883(2)°, V=893.29(18) Å^3, Z=2, D_{calcd}=1.369 Mg/m^3, $R1$=0.0530, w$R2$=0.1271(for observed data), $R1$=0.0997, w$R2$=0.1497 for all data. CCDC No. **1031463**. Crystal data of product **3**: $C_{26}H_{21}O_{10}Cl_3$, Mol. wt 599.78, Wavelength=0.71073 Å, Triclinic, P –1, a=10.2578(6) Å, b=11.3926(7) Å, c=12.2822(8) Å, α=81.982(5)°, β=70.581(6)°, γ=88.829(5)°, 1339.93(15), Z=2, D_{calcd}=1.487 Mg/m^3, $R1$=0.0634, w$R2$=0.1608 (for observed data), $R1$=0.1190, w$R2$=0.1991for all data. CCDC No. **1042107**. Crystal data of product **5**: $C_{17}H_{16}O_5$, Mol. wt 300.30, Wavelength=0.71073 Å, Monoclinic, P $2_1/n$, a=7.5830(12) Å, b=21.906(3) Å, c=8.8695(11) Å, β=92.687(5)°, V=1471.7(4) Å^3, Z=4, D_{calcd}=1.355 Mg/m^3, $R1$=0.0378, w$R2$=0.0930(for observed data), $R1$=0.0493, w$R2$=0.1004 for all data. CCDC No. **1031468**. Crystal data of product **6**: $C_{10}H_7NO_5$, Mol. wt 221.17, Wavelength=0.71073 Å, Monoclinic, $P2_1/c$, a=9.5664(11) Å, b=6.2063(6) Å, c=16.561(2) Å, β=104.283(6)°, V=952.87(19) Å^3, Z=4, D_{calcd}=1.542 Mg/m^3, $R1$=0.0406, w$R2$=0.1064 (for observed data), $R1$=0.0573, w$R2$=0.1197 for all data. CCDC No. **1031462**. Crystal data of product **7**: $C_{15}H_{16}O_7$, Mol. wt 308.28, Wavelength=0.71073 Å, Monoclinic, $P2_1/c$, a=7.9848(8) Å, b=16.773(2) Å, c=11.0114(15) Å, β=98.838(7)°, 1457.2(3) Å^3, Z=4, D_{calcd}=1.401 Mg/m^3, $R1$=0.0566, w$R2$=0.1424 (for observed data), $R1$=0.0867, w$R2$=0.1625 for all data. CCDC No. **1031466**. The tables of important H-bonding interactions of all products are given in Supplementary data.
15. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G. In *Vogel's Text Book of Practical Organic Chemistry Addition Wesley Longman Limited: England, 1989*.

Tetrahedron Letters 57 (2016) 4464–4467

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iodine–ammonium acetate promoted reaction between 2-aminopyridine and aryl methyl ketones: a novel approach towards the synthesis of 2-arylimidazo[1,2-*a*]pyridines

Dilpreet Kour, Rajni Khajuria, Kamal K. Kapoor *

Department of Chemistry, University of Jammu, Jammu 180 006, India

ARTICLE INFO

Article history:
Received 21 July 2016
Revised 16 August 2016
Accepted 18 August 2016
Available online 24 August 2016

Keywords:
Intramolecular cyclization
Ortoleva–King intermediate
2-Aminopyridine
Aryl methyl ketones
NH_4OAc
2-Arylimidazo[1,2-*a*]pyridines

ABSTRACT

I_2–NH_4OAc was found to be an efficient system for the metal-free synthesis of diversely substituted imidazo[1,2-*a*]pyridines **3a**–**r** from 2-aminopyridine **1** and aryl methyl ketones **2a**–**r** in one pot. 2-Arylimidazo[1,2-*a*]pyridines **3a**–**r** were obtained in good to excellent yields via in situ generation of an Ortoleva–King intermediate (pyridinium iodide), followed by NH_4OAc-assisted cyclization.

Imidazo[1,2-*a*]pyridines are indispensable biologically active nitrogen containing heterocyclic scaffolds and exhibit a wide range of biological activities.[1] These are broadly investigated in materials science and organometallics.[2] Imidazo[1,2-*a*]pyridines are recognized as a 'privileged scaffold' because these have significant importance in pharmaceutical industry owing to their interesting biological activities such as anti-cancer,[3] anti-viral,[4] anti-inflammatory,[5] analgesic, anti-pyretic,[6] anti-ulcer[7] and anti-bacterial.[8] Prospective radio ligands for positron emission tomography (PET) for β-amyloid in Alzheimer's disease based on imidazo[1,2-*a*] derivatives have been widely reported.[9] They also act as GABA and benzodiazepine receptor agonists[10] and cardiotonic agents.[11] These structures are also found in clinical drugs such as alpidem,[12] zolpidem,[10] olprinone,[13] zolimidine[6] and anti-HIV drug (GSK812397),[14] (Fig. 1). Furthermore, 2-(2-hydroxy phenyl)imidazo[1,2-*a*]pyridines exhibit excellent excited state intramolecular proton transfer (ESIPT)[15] thereby embracing significance in the field of optoelectronics. Prevalence of these skeletons in biologically active compounds continues to give chemists a momentum to develop novel methods for their synthesis.

Owing to the attractive properties of imidazo[1,2-*a*]pyridines, various methods to synthesize this core have been developed and reviewed.[16a–c] Initial coupling reaction of endocyclic nitrogen of 2-aminopyridine with various reagents such as acetophenones,[16d] α-haloketones,[16e] nitroalkenes,[16f] α-diazoketones,[16g] alkynes derivatives[16h] etc followed by cyclization via exocyclic amino group generates a variety of imidazo[1,2-*a*]pyridines. These reactions occur in the presence of various Bronsted or Lewis acids,[17,18] metal catalysts (Cu,[19] Fe,[20] Zn,[21]) and a carbocatalyst graphene oxide.[22] Few literature reports are available for the synthesis of 2-arylimidazo[1,2-*a*]pyridines from 2-aminopyridine and aryl methyl ketones via in situ generation of pyridinium iodide, first reported by Ortoleva[23] and King.[24] One of these reports has explored the I_2 catalysed Ortoleva–King reaction in combination with a strong base NaOH[25] for the intramolecular cyclization of pyridinium iodide to access *o*-hydroxy substituted 2-arylimidazo [1,2-*a*]pyridines with a limited substrate scope while the other reports make use of copper containing catalytic systems such as $CuI/In(CF_3SO_3)_3$[26] and I_2/CuO.[19d] These methods are suitable for a variety of substrates but suffer from one or more disadvantages such as high cost, long reaction time, inert and anhydrous conditions, low yields, tedious workup and product purification procedures. In view of these drawbacks and our quest to develop efficient and milder methods,[27] we contemplated the replacement of the stronger base NaOH with milder NH_4OAc in the Stasyuk's protocol.[25]

Ammonium acetate is known to be a mild base for effective Knoevenagel condensation[28] and has also been demonstrated as

* Corresponding author. Tel.: +91 191 2453969; fax: +91 191 2450014/2431365.
E-mail address: kamalkka@gmail.com (K.K. Kapoor).

http://dx.doi.org/10.1016/j.tetlet.2016.08.058
0040-4039/

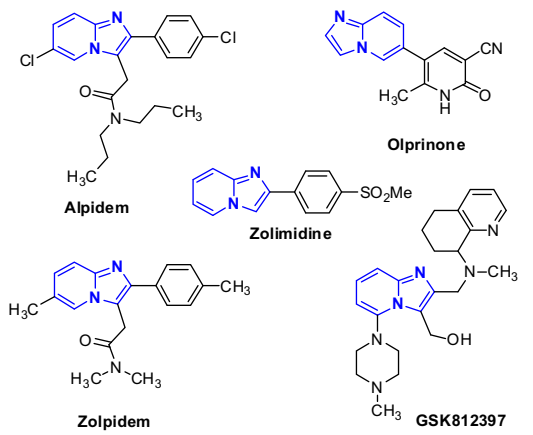
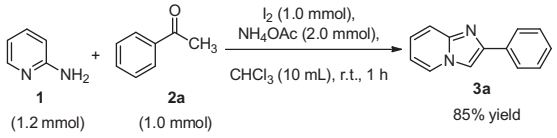


Figure 1. Bioactive drugs containing imidazo[1,2-*a*]pyridine nucleus.



Scheme 1. Synthesis of 2-phenylimidazo[1,2-*a*]pyridine **3a**.

an important source of ammonia in the synthesis of various heterocyclic scaffolds.[29] Further, iodine-catalysed reactions are found to be highly efficient alternatives in C—N bond formation as compared to transition metal-catalysed reactions and therefore have attracted great interest of synthetic chemists. Iodine is inexpensive, readily available,[30] environmentally-benign as compared to transition metal catalysts[31] and operates under mild conditions.[32] Further, most iodine catalysed reactions involve domino reaction sequences[33] forming several bonds in a single operation thereby imparting molecular diversity and complexity among the compounds synthesized. Some of the well-known reactions include one-pot synthesis of 2-acylbenzothiazoles via iodine promoted domino oxidative cyclization,[34] one-pot synthesis of pyrrolo[1,2-*a*]quinoxaline and imidazo[1,5-*a*]quinoxaline derivatives via sp^3 and sp^2 C—H dehydrogenative coupling,[35] divergent synthesis of benzimidazoles, dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines,[36] oxidative esterification of *o*-alkynylaldehydes,[37] one-pot synthesis of 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*] pyridines from alkylaryl ketones and 2-aminopyridines.[38]

One-pot reaction is much desired by the chemists because it saves time and resources by eliminating the separation processes for purification of the chemical intermediates and also improves the overall yield. We wished to develop a one-pot method for the synthesis of 2-arylimidazo[1,2-*a*]pyridines by the condensation of 2-aminopyridine with various arylmethyl ketones using Ortoleva–King conditions followed by intramolecular cyclization with NH_4OAc.

The preliminary investigation was performed using 2-aminopyridine **1** and acetophenone **2a** as the model substrates. The initial reaction between 2-aminopyridine **1** (1.2 mmol), acetophenone **2a** (1.0 mmol), I_2 (1.0 mmol) and NH_4OAc (2.0 mmol) in $CHCl_3$ at room temperature for 1 h led to the formation of the desired product 2-phenylimidazo[1,2-*a*]pyridine[39] **3a** in 85% yield (Scheme 1).

During this study, a comparison between the literature methods (entries 1–6)[19c,d,25,26,39,40] and present work (entries 7–10) was made and it became evident from the Table 1 that our reaction conditions (entry 7) were milder with better or comparable yields. Different ratios of iodine and ammonium acetate to effect this reaction (entries 7–10) revealed the optimum requirement as the usage of 1 and 2 equiv of I_2 and NH_4OAc with respect to ketone (entry 7, 85% yield).

Replacement of NH_4OAc with NH_4OH, NH_4HCO_3, $NH_4H_2PO_4$, $(NH_4OOCH)_2$, $NH_4(OOCH)$, $(NH_4)_2CO_3$, NH_4Cl, NH_4NO_3, NH_4SCN, Et_3N or DMAP as well as $CHCl_3$ with CH_3CN, 1,2-DCE, DMF, EtOH, *n*-BuOH or toluene did not prove beneficial toward product yield.

Under the optimized conditions, diversely substituted aryl methyl ketones were investigated[41] and the results are summarized in Table 2. It was also noticed that for some sterically hindered and electron rich substrates (entries **2i**, **2n**–**q**), better yields were obtained under reflux. Aryl methyl ketones bearing electron donating (Me, OMe), electron withdrawing groups (F, Cl, NO_2) as well as disubstitution in the phenyl ring generated the corresponding 2-arylimidazo[1,2-*a*]pyridines (entries **3a**–**m**) in good to excellent yields (63–85%). Further, to establish the generality of the reaction, furan-2-yl/thiophen-2-yl methyl ketones were investigated and smooth formation of the corresponding furan-2-yl/thiophen-2-yl substituted imidazo[1,2-*a*]pyridines (entries **3n**–**o**) was observed with good yields (77–79%). The construction of imidazo[1,2-*a*]pyridines bearing bi-cyclic substitutions (entries **3p**–**q**) was also achieved under these optimized conditions. Interestingly, 3-acetyl-2*H*-chromen-2-one led to the formation of 3-(imidazo[1,2-*a*]pyridin-2-yl)-2*H*-chromen-2-one, a hybrid of imidazo[1,2-*a*]pyridine and coumarin (entry **3q**, 80% yield). The 2-aminopyridine with a methyl group in the 3-position smoothly underwent the reaction, and product (entry **3r**) was obtained in an appreciable 82% yield.

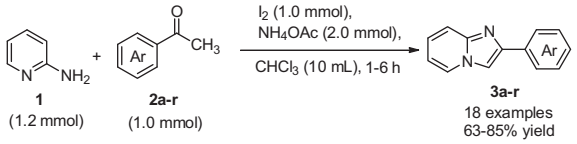
In line with the mechanism proposed by Zhang et al.,[42] following mechanism is proposed for the synthesis of 2-arylimidazo[1,2-*a*]pyridines **3a**–**r** as illustrated in Scheme 2.

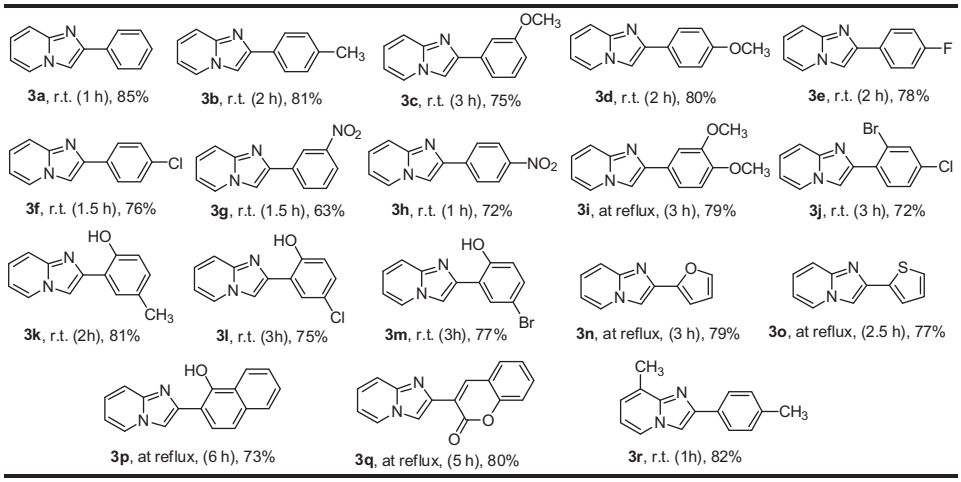
Table 1
Comparison of model reaction with literature reports[a]

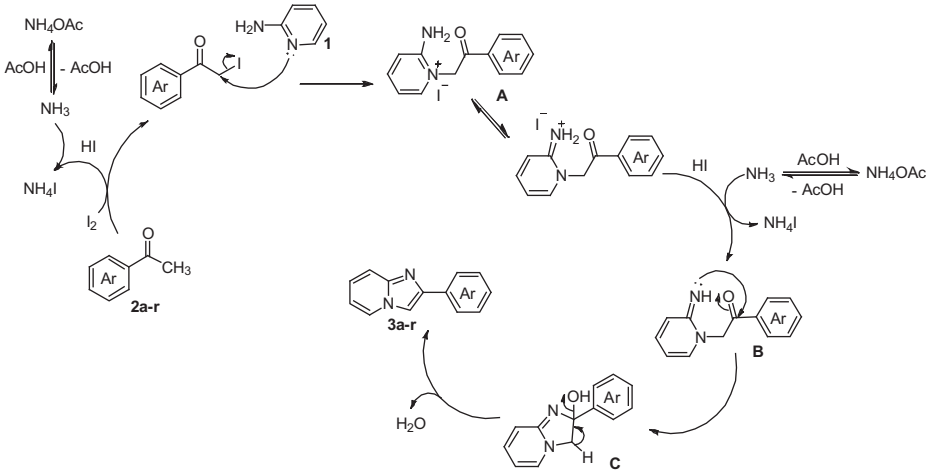
Entry	Catalyst	Ligand (10 mol %)	Additive	Solvent	Oxidant	Temp (°C)/time (h)	Yield (%)[b]
1	$Cu(OAc)_2{\cdot}H_2O$ (0.1 equiv)	1,10-Phenanthroline	ZnI_2 (0.1 equiv)	Dichlorobenzene	O_2 (1 atm)	120/24	84[39]
2	CuI (0.2 equiv)	—	—	1,4-Dioxane	—	100/14	71[19c]
3[c]	CuI (0.2 equiv)	—	$BF_3{\cdot}Et_2O$ (0.1 equiv)	Neat	O_2 (1 atm)	40/24	70[40]
4[d]	CuI (0.05 equiv)	—	In $(CF_3SO_3)_3$ (0.01 equiv)	NMP	O_2 (1 atm)	100/30	81[26]
5	Iodine (1.2 equiv)	—	Aq NaOH (45%)	—	—	100–110	55[25]
6[e]	Iodine (1.1 equiv)	—	CuO (1.1 equiv)	MeOH	—	Reflux/12	82[19d]
7	**Iodine (1.0 equiv)**	—	**NH_4OAc (2.0 equiv)**	**$CHCl_3$**	—	**rt/1**	**85**
8	Iodine (2.0 equiv)	—	NH_4OAc (2.0 equiv)	$CHCl_3$	—	rt/1	80
9	Iodine (1.0 equiv)	—	NH_4OAc (3.0 equiv)	$CHCl_3$	—	rt/1	82
10	Iodine (0.5 equiv)	—	NH_4OAc (1.0 equiv)	$CHCl_3$	—	rt/1	63

Bold values indicate optimized reaction conditions.
[a] Reaction conditions: **1** (1.2 equiv), **2a** (1.0 equiv), at a given temperature and time.
[b] Isolated yields.
[c] **2a** (3.0 equiv) was used.
[d] **2a** (2.0 equiv) was used.
[e] **1** (1.0 equiv) was used.

Table 2
I_2–NH_4OAc promoted synthesis of 2-arylimidazo[1,2-*a*]pyridines **3a–r**







Scheme 2. Plausible mechanism for the formation of 2-arylimidazo[1,2-*a*]pyridines **3a–r** with I_2–NH_4OAc.

The first step involves the reaction of pyridine endocyclic nitrogen with the α-carbon of in situ generated α-iodoketone leading to the formation pyridinium salt **A**. Intramolecular cyclization of the imine **B** generated by the deprotonation of **A** gives tetrahydroimidazo[1,2-*a*]pyridin-2-ol **C**, which upon elimination of water resulted in the formation of 2-arylimidazo[1,2-*a*]pyridines **3a–r**. HI produced during the reaction is believed to be scavenged by NH_3 produced from NH_4OAc.

In summary, we have developed an efficient, metal-free synthesis of diversely substituted 2-arylimidazo[1,2-*a*]pyridines showing versatility in terms of milder reaction conditions and easy product purification avoiding the use of column chromatography.

Acknowledgments

The authors are thankful to University Grants Commission (UGC), New Delhi for funding (Project No. MRP-MAJOR-CHEM-2013-21745). R.K. further acknowledges UGC, New Delhi for Senior Research Fellowship.

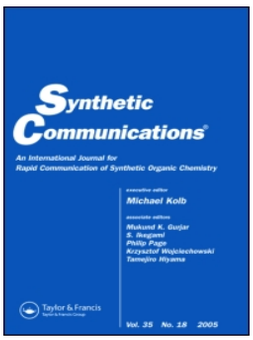
Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.058.

References and notes

1. Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; Clercq, E. D.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271.
2. (a) Wan, J.; Zheng, C. J.; Fung, M. K.; Liu, X. K.; Lee, C. S.; Zhang, X. H. *J. Mater. Chem.* **2012**, *22*, 4502; (b) Gueiffier, C. E.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888; (c) John, A.; Shaikhand, M. M.; Ghosh, P. *Dalton Trans.* **2009**, 10581; (d) Song, G.; Zhang, Y.; Li, X. *Organometallics* **2008**, *27*, 1936; (e) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743.

3. Hamdouchi, C.; Blas, J. D.; Prado, M. D.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50.
4. Elkakmaoui, A.; Gueiffier, A.; Milhavet, J. C.; Blache, Y. J.; Chapat, P.; Chavignon, O.; Teulade, J. C.; Snoeck, R.; Andrei, G.; Clerc, E. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1937.
5. Lacerda, R. B.; de Lima, C. K. F.; da Silva, L. L.; Romeiro, N. C.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2009**, *17*, 74.
6. Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305.
7. Kaminski, J. J.; Doweyko, A. M. *J. Med. Chem.* **1997**, *40*, 427.
8. Byth, K. F.; Culshaw, J. D.; Green, S.; Oakes, S. E.; Thomas, A. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2245.
9. Cai, L.; Chin, F. T.; Pike, V. W.; Toyama, H.; Liow, J. S.; Zoghbi, S. S.; Modell, K.; Briard, E.; Shetty, H. U.; Sinclair, K.; Donohue, S.; Tipre, D.; Kung, M. P.; Dagostin, C.; Widdowson, D. A.; Green, M.; Gao, W.; Herman, M. M.; Ichise, M.; Innis, R. B. *J. Med. Chem.* **2004**, *47*, 2208.
10. Humphries, A. C.; Gancia, E.; Gilligan, M. T.; Goodacre, S.; Hallett, D.; Merchant, K. J.; Thomas, S. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1518.
11. Davey, D.; Erhardt, P. W.; Lumma, W. C.; Wiggins, J. J.; Sullivan, M.; Pang, D.; Cantor, E. *J. Med. Chem.* **1987**, *30*, 1337.
12. Jain, A. N. *J. Med. Chem.* **2004**, *47*, 947.
13. Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. *Cardiovasc. Drug Rev.* **2002**, *20*, 163.
14. Boggs, S.; Elitzin, V. I.; Gudmundsson, K.; Martin, M. T.; Sharp, M. J. *Org. Process Res. Dev.* **2009**, *13*, 781.
15. (a) Douhal, A.; Guerri, F. A.; Acuna, A. U. *J. Phys. Chem.* **1995**, *99*, 76; (b) Douhal, A.; Guerri, F. A.; Acuiia, A. U. *Angew. Chem., Int. Ed.* **1997**, *36*, 1514.
16. (a) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun.* **2015**, 1555; (b) Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A. *Synthesis* **2015**, *47*, 887; (c) Koubachi, J.; Kazzouli, S. E.; Bousmina, M.; Guillaumet, G. *Eur. J. Org. Chem.* **2014**, 5119; (d) Meng, X.; Yu, C.; Chen, G.; Zhao, P. *Catal Sci. Technol.* **2015**, *5*, 372; (e) Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H.; Smith, I. E. D. *Org. Biomol. Chem.* **2012**, *10*, 1093; (f) Yan, H.; Yang, S.; Gao, X.; Zhou, K. C.; Ma, C.; Yan, R.; Huang, G. *Synlett* **2012**, 2961; (g) Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. *Tetrahedron Lett.* **2007**, *48*, 7717; (h) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, 11073.
17. Ge, W.; Zhu, X.; Wei, Y. *Eur. J. Org. Chem.* **2013**, 6015.
18. Yan, H.; Wang, Y.; Pan, C.; Zhang, H.; Yang, S.; Ren, X.; Li, J.; Huang, G. *Eur. J. Org. Chem.* **2014**, 2754.
19. (a) Yan, R. L.; Yan, H.; Ma, C.; Ren, Z. Y.; Gao, X. A.; Huang, G. S.; Liang, Y. M. *J. Org. Chem.* **2012**, *77*, 20248; (b) Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.* **2012**, *14*, 1688; (c) Pericherla, K.; Kaswan, P.; Khedar, P.; Khungar, B.; Parang, K.; Kumar, A. *RSC Adv.* **2013**, *3*, 18923; (d) Cai, Q.; Liu, M. C.; Mao, B. M.; Xie, X.; Jia, F. C.; Zhu, Y. P.; Wu, A. X. *Chin. Chem. Lett.* **2015**, *26*, 881.
20. Santra, S.; Bagdi, A. K.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1065.
21. Liu, P.; Deng, C. L.; Lei, X.; Lin, G. Q. *Eur. J. Org. Chem.* **2011**, 7308.
22. Kundu, S.; Basu, B. *RSC Adv.* **2015**, *5*, 50178.
23. Ortoleva, G. *Gazz. Chim. Ital.* **1899**, *29*, 503.
24. (a) King, L. C. *J. Am. Chem. Soc.* **1944**, *66*, 894; (b) King, L. C.; Mcwhirter, M.; Rowland, R. L. *Am. Chem. Soc.* **1948**, *70*, 239.
25. Stasyuk, A. J.; Banasiewicz, M.; Cyranski, M. K.; Gryko, D. T. *J. Org. Chem.* **2012**, *77*, 5552.
26. Zhang, Y.; Chen, Z.; Wu, W.; Zhang, Y.; Su, W. *J. Org. Chem.* **2013**, *78*, 12494.
27. (a) Naqvi, T.; Mahajan, D.; Sharma, R. L.; Khan, I. A.; Kapoor, K. K. *J. Heterocycl. Chem.* **2011**, *48*, 144; (b) Khajuria, R.; Saini, Y.; Kapoor, K. K. *Tetrahedron Lett.* **2013**, *54*, 5699; (c) Saini, Y.; Khajuria, R.; Rana, L. K.; Hundal, M. S.; Gupta, V. K.; Kant, R.; Kapoor, K. K. *Tetrahedron* **2016**, *72*, 257.
28. Kumar, H. M. S.; Subbareddy, B. V.; Anjaneyuluand, S.; Yadav, J. S. *Synth. Commun.* **1998**, *28*, 3811.
29. (a) Khajuria, R.; Kannaboina, P.; Kapoor, K. K.; Gupta, A.; Raina, G.; Jassal, A. K.; Rana, L. K.; Hundal, M. S.; Das, P. *Org. Biomol. Chem.* **2015**, *13*, 5944; (b) Khajuria, R.; Dham, S.; Kapoor, K. K. *RSC Adv.* **2016**, *6*, 37039.
30. (a) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, 11333; (b) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754.
31. (a) Wan, C.; Gao, L.; Wang, Q.; Zhang, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 3902; (b) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.
32. (a) Zhu, Y. P.; Liu, M. C.; Jia, F. C.; Yuan, J. J.; Gao, Q. H.; Lian, M.; Wu, A. X. *Org. Lett.* **2012**, *14*, 3392; (b) Gao, Q.; Wu, X.; Li, Y.; Liu, S.; Meng, X.; Wu, A. *Adv. Synth. Catal.* **2014**, *356*, 2924; (c) Tang, S.; Wu, Y.; Liao, W.; Bai, R.; Liu, C.; Lei, A. *Chem. Commun.* **2014**, 4496.
33. (a) Zeng, L. Y.; Cai, C. *J. Comb. Chem.* **2010**, *12*, 35; (b) Zalavadiya, P.; Tala, S.; Akbari, J.; Joshi, H. *Arch. Pharm. Chem. Life Sci.* **2009**, *342*, 469.
34. Zhu, Y. P.; Lian, M.; Jia, F. C.; Liu, M. C.; Yuan, J. J.; Gao, Q. H.; Wu, A. X. *Chem. Commun.* **2012**, 9086.
35. Zhang, Z.; Xie, C.; Tan, X.; Song, G.; Wen, L.; Gao, H.; Ma, C. *Org. Chem. Front.* **2015**, *2*, 942.
36. Naresh, G.; Kant, R.; Narender, T. *J. Org. Chem.* **2014**, *79*, 3821.
37. Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.
38. Fei, Z.; Zhu, Y. P.; Liu, M. C.; Jia, F. C.; Wu, A. X. *Tetrahedron Lett.* **2013**, *54*, 1222.
39. Bagdi, A. K.; Rahman, M.; Santra, S.; Majee, A.; Hajra, A. *Adv. Synth. Catal.* **2013**, *355*, 1741.
40. Cai, Z. J.; Wang, S. Y.; Ji, S. J. *Adv. Synth. Catal.* **2013**, *355*, 2686.
41. *Procedure for the synthesis of 2-arylimidazo[1,2-a]pyridines* (**3a–r**): A mixture of 2-aminopyridine **1** (1.2 mmol), aryl methyl ketone **2a–r** (1.0 mmol), I_2 (1.0 mmol) and NH_4OAc (2.0 mmol) in $CHCl_3$ (10 mL) in a 25 mL round-bottomed flask was stirred at room temperature until the completion of reaction (Table 2). The reaction mixture was further diluted with 20 mL of $CHCl_3$, washed with saturated solution of $Na_2S_2O_3$ (2×10 mL), water (1×10 mL), brine (1×10 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed and the residue after recrystallisation with EtOH afforded the desired 2-arylimidazo[1,2-*a*]pyridines (**3a–r**, 63-85%). For entries **2i** and **2n–q**, reaction was performed under reflux.
42. Wang, F.-J.; Xu, H.; Xin, M.; Zhang, Z. *Mol. Divers.* **2016**, *20*, 659.



Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Synthesis and antimicrobial evaluation of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and their 2-thioxo analogues

Yeshwinder Saini, Rajni Khajuria, Ramneet Kaur, Sanjana Kaul, Tanwi Sharma, Suruchi Gupta, Vivek K. Gupta, Rajni Kant & Kamal K. Kapoor

To cite this article: Yeshwinder Saini, Rajni Khajuria, Ramneet Kaur, Sanjana Kaul, Tanwi Sharma, Suruchi Gupta, Vivek K. Gupta, Rajni Kant & Kamal K. Kapoor (2017) Synthesis and antimicrobial evaluation of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and their 2-thioxo analogues, Synthetic Communications, 47:12, 1159-1168, DOI: 10.1080/00397911.2017.1316407

To link to this article: https://doi.org/10.1080/00397911.2017.1316407

SYNTHETIC COMMUNICATIONS®
2017, VOL. 47, NO. 12, 1159–1168
https://doi.org/10.1080/00397911.2017.1316407

Taylor & Francis
Taylor & Francis Group

Synthesis and antimicrobial evaluation of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones and their 2-thioxo analogues

Yeshwinder Saini[a], Rajni Khajuria[a], Ramneet Kaur[a], Sanjana Kaul[b], Tanwi Sharma[b], Suruchi Gupta[b], Vivek K. Gupta[c], Rajni Kant[c], and Kamal K. Kapoor[a]

[a]Department of Chemistry, University of Jammu, Jammu, India; [b]School of Biotechnology, University of Jammu, Jammu, India; [c]X-ray Crystallography Laboratory, Department of Physics and Electronics, University of Jammu, Jammu, India

ABSTRACT

The preparation of some novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **8(i–xiv)** and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-ones **9(i–xiv)** have been reported through one-pot catalyst-free reaction of aldehydes, semicarbazide hydrochloride/thiosemicarbazide with ninhydrin. All the synthesized compounds have been screened for antimicrobial activity and some of them were observed to possess broad spectrum antibacterial potential as well as significant antagonistic potential against fungal pathogens.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 13 February 2017

KEYWORDS
Antibacterial; antifungal; ninhydrin; tetrahydroindenoimidazole-dione; 2-thioxotetrahydro indenoimidazolone

Introduction

Hydrazones (semicarbazones and thiosemicarbazones) **1** play a significant role in the synthesis of biologically important heterocyclic compounds.[1] They are of immense biological significance and are known to exhibit anticancer,[2] antimalarial,[3] antiviral,[4] antifungal,[5] antibacterial,[6] antitubercular,[7] and anti-inflammatory[8] properties. Ninhydrin has been used in the synthesis of a variety of biologically active imidazole derivatives.[9] For example, compound **2** obtained by the reaction of ninhydrin with thiourea exhibited promising antimicrobial activity against Gram-positive and Gram-negative bacteria and a fungus *Candida albicans*.[10] Compound **3**, a hydrophobic

CONTACT Sanjana Kaul sanrozie@rediffmail.com School of Biotechnology, University of Jammu - 180006, Jammu, India; Kamal K. Kapoor k2kapoor@yahoo.com Department of Chemistry, University of Jammu - 180006, Jammu, India.
Color versions of one or more of the figures in this article can be found online on at www.tandfonline.com/lsyc
Supplemental data (experimental data, X-ray crystallographic data, ^{1}H NMR and ^{13}C NMR spectra of all the synthesized compounds) can be accessed on the publisher's website.

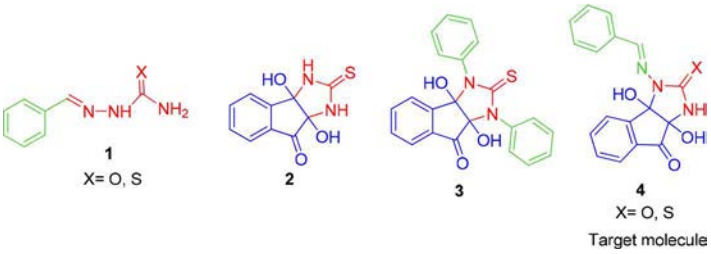


Figure 1. Design of prototype.

analogue of **2**, is devoid of two H-bond donors. Obtained[11] by the reaction of ninhydrin with diphenylthiourea, compound **3** has shown improvement in activity against some bacterial strains (*Bacillus subtilis, Streptococcus pneumoniae, Pseudomonas aeruginosa*) and loss against some other strains (*Shigella flexneri, Escherichia coli*). Loss in antifungal activity of compound **3** against *C. albicans* was also noticed.[10,11] In view of this irregular trend in activity, we wished to maintain a balance between hydrophilicity and hydrophobicity by retaining one H-bond donor and this led us to design a compound **4** possessing the attributes of hydrazones as well as tetrahydroindeno[1,2-*d*]imidazolones (Fig. 1).

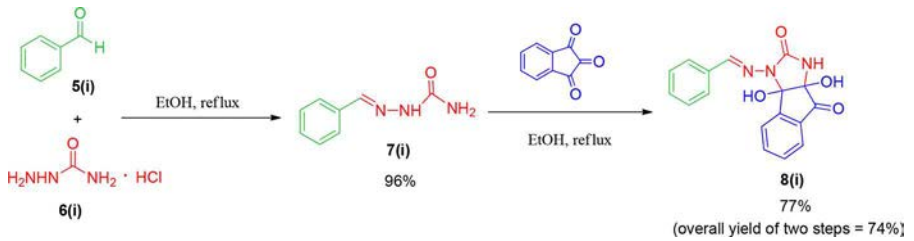
Results and discussion

Chemistry

Benzaldehyde **5(i)** (1 mmol) was reacted with semicarbazide hydrochloride **6(i)** (1 mmol) in ethanol to yield the corresponding semicarbazone **7(i)** (96%), which upon reaction with ninhydrin (1.2 mmol) in ethanol (thin-layer chromatography, TLC) at reflux led to the formation of 3-(benzylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*] imidazole-2,8-dione **8(i)** (77%) (overall yield 74%) (Scheme 1).

In another set of experiment, one-pot reaction was performed. Initially, benzaldehyde **5(i)** (1 mmol) and semicarbazide hydrochloride **6(i)** (1 mmol) were reacted in refluxing ethanol (30 min) and noticing the completion of reaction (TLC), ninhydrin (1.2 mmol) was added and refluxing was continued. After 90 min, the reaction got completed and 8% increase in the yield of the desired product **8(i)** was noticed. Replacing ethanol with various solvents (Table 1) led us to conclude that 1,4-dioxane was the best solvent for this reaction.

Further, replacement of semicarbazide hydrochloride **6(i)** with thiosemicarbazide **6(ii)** yielded the expected 3-(benzylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,



Scheme 1. Synthesis of 3-(benzylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*] imidazole-2,8-dione **8(i)**.

Table 1. Optimization of solvent.

Entry	Solvent	Yield (%)
1	CH_3CN	80
2	**1,4-Dioxane**	**90**
3	1,2-DCE	77
4	DMF	70
5	Toluene	72
6	THF	75
7	Benzene	73
8	EtOH	82

Bold values and terms signify the best conditions found.

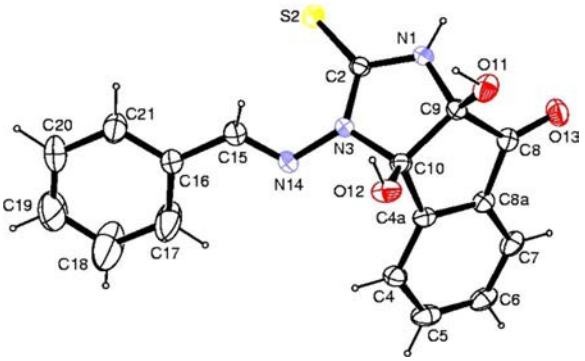


Figure 2. ORTEP diagram of 3-(benzylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno [1,2-*d*] imidazol-8(2*H*)-one **(9i)**.

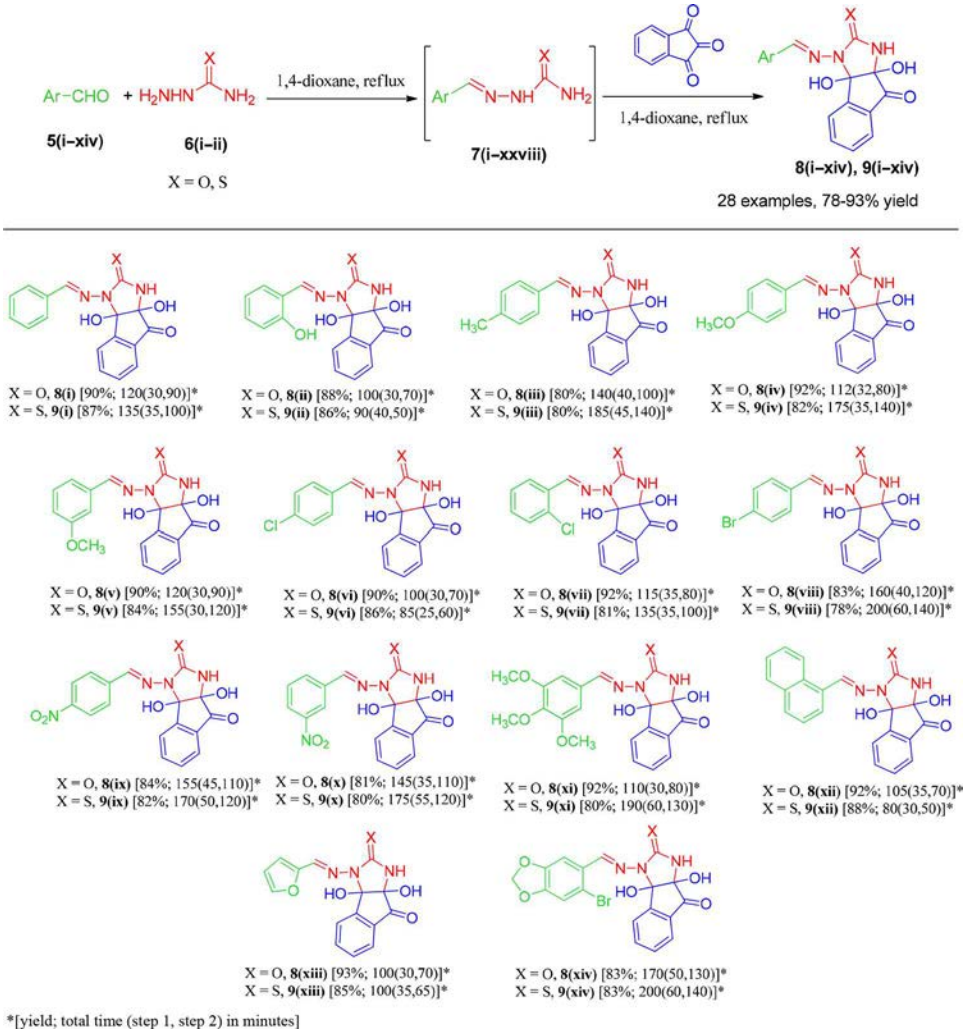
8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-one **9(i)** in 87% yield. The structure of **9(i)** was supported by single-crystal X-ray crystallographic study (Fig. 2). The Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of **9(i)** clearly indicates that the two hydroxyl groups are in *cis*-conformation.

A variety of aromatic aldehydes bearing electron-donating and electron-withdrawing groups led to the successful formation of the desired products **8(i–xiv)** and **9(i–xiv)** (Scheme 2). The plausible mechanism for the formation of 3-(arylideneamino)-3a, 8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **8(i–xiv)** and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-ones **9(i–xiv)** is shown in Scheme 3. The terminal nitrogen of semi/thiosemicarbazone **7(i–xxviii)**, formed *in situ*, underwent nucleophilic addition reaction with ninhydrin to form hydrazine carboxamide/carbothioamide intermediate (**A**) and this was followed by attack from the same side of the internal nitrogen to yield the desired *cis*-products **8(i–xiv)/9(i–xiv)** as illustrated in Scheme 3. It is pertinent to mention that attack from the same side lead to the exclusive formation of *cis*-product, since it is well established[12] that *cis*-biquinane systems are far more stable than their *trans*-counterparts.

Biological evaluation

*Antibacterial and antifungal bioassays (*in vitro*)*

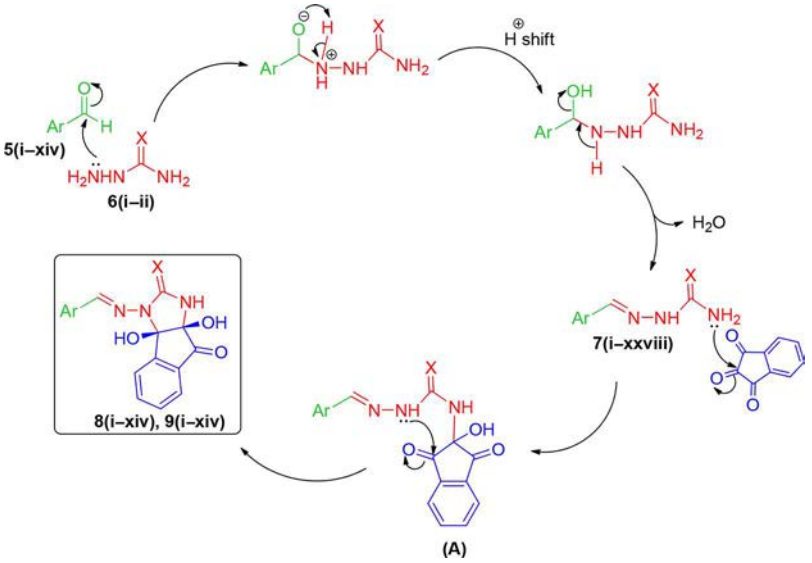
The antibacterial screening of the test compounds **8(i–xiv)** and **9(i–xiv)** was performed against eight bacterial strains at concentrations of 100, 250, 500, 750, and 1000 μg mL^{-1}.



Scheme 2. One-pot synthesis of indeno-3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **8(i–xiv)** and their 2-thioxo analogues **9(i–xiv)**.

No inhibitory activity was observed for the test compounds at 100, 250, 500, and 750 μg mL^{-1}. At 1000 μg mL^{-1} concentration, the test compounds displayed perceptible potential against the screened bacterial strains (Table 2, Fig. 3). The results clearly indicate that 24 out of the 28 compounds showed activity against one or more strains. Compounds **8(viii, xii)** and **9(v)** possessed broad spectrum antibacterial activity against all the tested strains, whereas **8(ix)** and **9(vi)** were found active against seven test cultures. **9(vii)** and **9(xii)** displayed moderate inhibitory potential against five tested strains. Compounds **8 (viii)** and **9(vi)** were active against four, **8(xii)** against three, **8(xiv)** against two and **8 (ix), 9(v), 9(x)**, and **9(xiii)** against one bacterial strain. Four compounds **8(v, x)** and **9 (xi, xiv)** did not exhibit antibacterial activity against any of the organisms screened.

Antifungal potential of the test compounds **8(i–xiv)** and **9(i–xiv)** was represented as percentage inhibition values (Table 3, Fig. 4). The investigation of antifungal screening



Scheme 3. Plausible mechanism for the formation of **8(i–xiv)** and **9(i–xiv)**.

Table 2. Antibacterial activity of test compounds **8(i–xiv)** and **9(i–xiv)**.

	Diameter of inhibition zone against pathogens (mm)							
Test compound	*B.s*	*B.c*	*S.a*	*K.p*	*E.c*	*E.f*	*P.a*	*P.al*
8(i)	—	10	11	—	9	12	—	—
8(ii)	12	11	12	—	—	—	11	—
8(iii)	—	13	11	—	—	—	—	11
8(iv)	11	—	—	12	10	—	12	—
8(v)	—	—	—	—	—	—	—	—
8(vi)	—	11	10	—	12	—	12	—
8(vii)	—	11	—	—	—	—	—	—
8(viii)	15	14	14	13	12	13	14	12
8(ix)	14	13	13	12	13	11	13	—
8(x)	—	—	—	—	—	—	—	—
8(xi)	—	—	11	—	11	—	—	—
8(xii)	12	11	15	14	13	12	15	11
8(xiii)	—	12	12	—	11	—	11	—
8(xiv)	15	—	14	—	12	9	—	—
9(i)	12	—	—	12	—	—	13	—
9(ii)	—	13	—	—	—	11	—	12
9(iii)	—	—	—	—	12	—	11	12
9(iv)	13	—	—	11	—	—	10	—
9(v)	13	14	12	12	11	13	13	13
9(vi)	13	—	14	15	13	15	16	11
9(vii)	12	11	13	—	—	12	13	—
9(viii)	—	—	12	—	10	—	12	13
9(ix)	13	12	—	—	11	—	12	—
9(x)	—	—	14	—	9	6	—	12
9(xi)	—	—	—	—	—	—	—	—
9(xii)	—	11	12	—	12	—	13	13
9(xiii)	12	—	13	—	—	14	—	—
9(xiv)	—	—	—	—	—	—	—	—
+ve Control (SD)	19	19	20	19	15	20	21	19
−ve Control	—	—	—	—	—	—	—	—

B.s, Bacillus subtilis; *B.c, Bacillus cereus*; *S.a, Staphylococcus aureus*; *K.p, Klebsiella pneumoniae*; *E.c, Escherichia coli*; *E.f, Enterococcus faecalis*; *P.a, Pseudomonas aeruginosa*; *P.al, Pseudomonas alcaligenes*.

+ve Control = chloramphenicol (at 100 µg mL^{-1} concentration); −ve Control = DMSO; test compounds (at 1000 µg mL^{-1} concentration).

"—" sign indicates the absence of clear zone; weaker = 6–10 mm; moderate = 10–13 mm, above 13 mm = good.

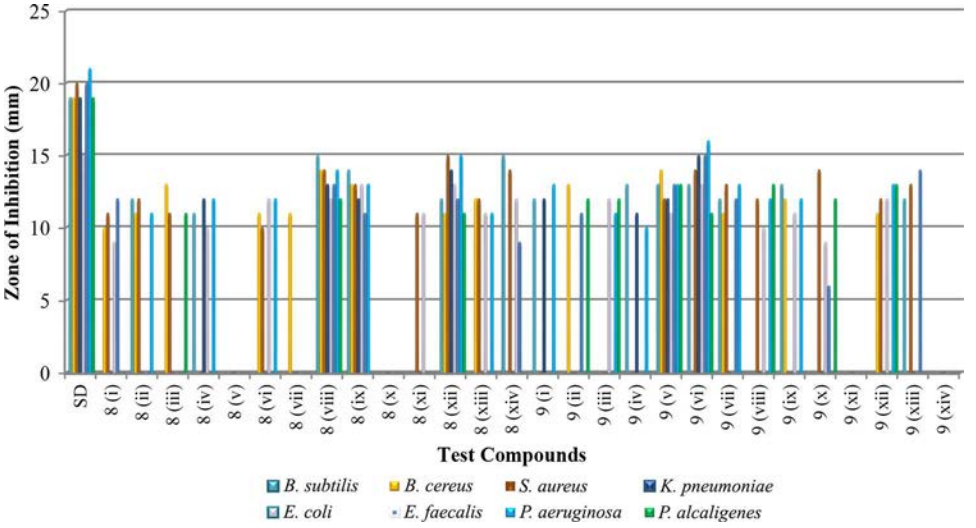


Figure 3. Comparison of antibacterial activity of **8(i–xiv)** and **9(i–xiv)** with the standard drug (chloramphenicol).

of these compounds revealed their varying degrees of activity against all the tested micro-organisms. Compound **9(viii)** exhibited a very good antifungal activity with 70 and 78% growth inhibition against *Fusarium oxysporum and Alternaria alternata*, respectively.

Table 3. Antifungal activity of test compounds **8(i–xiv)** and **9(i–xiv)**.

	% inhibition of test fungal pathogens	
Test compound	*Fusarium oxysporum*	*Alternaria alternate*
8(i)	24.21	52.86
8(ii)	43.22	64.28
8(iii)	41.00	51.57
8(iv)	51.67	67.14
8(v)	58.00	21.24
8(vi)	17.21	68.00
8(vii)	29.70	34.28
8(viii)	47.22	71.43
8(ix)	21.90	2.86
8(x)	21.12	—
8(xi)	29.00	62.14
8(xii)	42.00	39.00
8(xiii)	29.33	64.28
8(xiv)	12.80	34.28
9(i)	31.21	19.32
9(ii)	38.63	33.12
9(iii)	54.00	60.00
9(iv)	40.00	43.00
9(v)	14.24	18.21
9(vi)	22.12	33.00
9(vii)	29.00	29.22
9(viii)	70.00	78.00
9(ix)	45.42	52.10
9(x)	37.61	32.70
9(xi)	39.80	32.32
9(xii)	32.12	36.00
9(xiii)	17.98	33.00
9(xiv)	49.5	36.43

Test compounds (at 1000 μg mL^{-1} concentration).

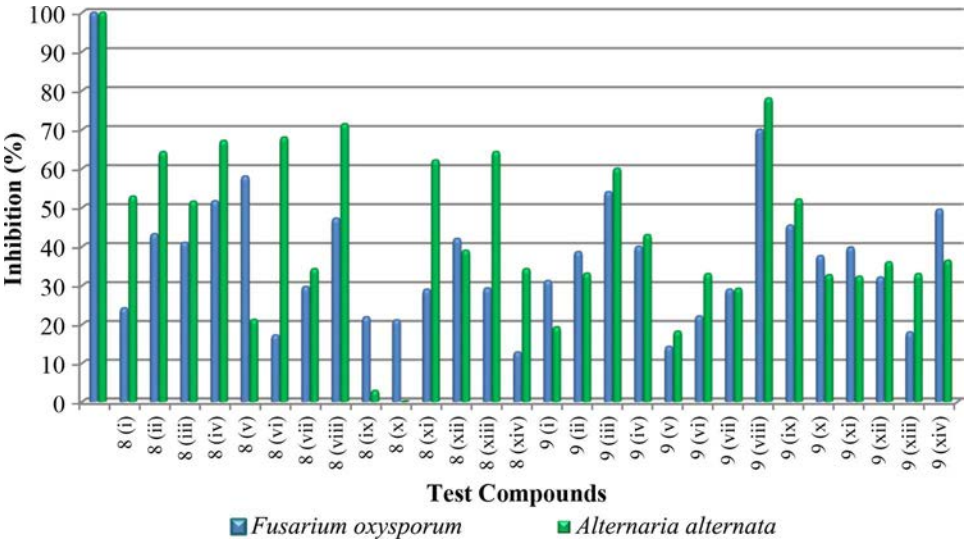


Figure 4. Antifungal potential of test compounds.

Compound **8(viii)** displayed 71.43% growth inhibition against *A. alternata*. Rest of the test compounds showed varying degrees of percentage inhibition of tested fungal pathogens ranging from 2.86 to 68%. Species of *Alternaria* and *Fusarium* are reported to cause broad spectrum infections in humans and mostly affect immune compromised patients. Therefore, the compounds showing significant activity against these fungi can serve as potential candidates for antifungal therapy.

Experimental

General

All the experiments were performed in an oven-dried glass apparatus. All the commercially available reagents were purchased from Aldrich and were used without further purification. Melting points (°C) were measured in open glass capillaries using Perfit melting point apparatus and are uncorrected. The progress of reaction was monitored by TLC using silica gel precoated aluminum sheets (60 F254, Merck). Visualization of spots was affected by exposure to ultraviolet (UV) light at 365 and 254 nm, iodine vapors, and 2% 2,4-dinitrophenylhydrazine solution in methanol containing few drops of H_2SO_4 and Dragendorff reagent. IR spectra (ν, cm^{-1}) were recorded on Perkin-Elmer FTIR spectrophotometer using KBr discs. ^1H and ^{13}C NMR were recorded on Bruker AC-400 spectrometer operating, respectively, at 400 and 100 MHz with tetramethylsilane (TMS) as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from TMS. *J* values are given in Hertz (Hz). The abbreviations s, bs, d, t, q, and m in ^1H NMR spectra refer to singlet, broad singlet, doublet, triplet, quartet, and multiplet, respectively. Electron impact mass spectra were recorded on Micro Mass VG-7070 H mass spectrometer at 70 eV. Elemental analysis was performed on Leco CHNS 932 analyzer. Solvents were removed using Heidolph rotary evaporator. Column chromatography was performed using a gradient of ethylacetate and petroleum ether.

The synthesized 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*] imidazole-2,8-diones **8(i–xiv)** and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-ones **9(i–xiv)** were screened for their *in vitro* antibacterial activity using agar well diffusion method.[13] The test pathogens used in the study included four Gram-positive bacteria [*B. subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 3160), *Klebsiella pneumoniae* (MTCC 109), *Bacillus cereus* (MTCC 430)], and four Gram-negative bacteria [*E. coli* (MTCC 40), *Enterococcus faecalis* (MTCC 439), *P. aeruginosa* (MTCC 1934), and *Pseudomonas alcaligenes* (MTCC 493)]. For antibacterial assay, test pathogens were revived by growing overnight at 37 °C and 100 rpm. Test compounds were prepared by dissolving in DMSO at concentrations of 100, 250, 500, 750, and 1000 μg mL^{-1}, whereas the standard drug chloramphenicol was used at a concentration of 100 μg mL^{-1}. DMSO was used as a negative control. Sterile Petri plates were poured with 35 mL of nutrient agar medium. A total of 100 μL of bacterial suspension was spread on the solidified plates. Wells were bored in the plates with the help of borer of 6 mm diameter. A total of 100 μL of prepared compounds was added to labeled wells. The results were observed as diameter of zone of inhibition after incubating the plates at 37 °C overnight.

Antifungal activity of these compounds was evaluated against *F. oxysporum* (MTCC 2485) and *A. alternata* (MTCC 2724) by poison food technique.[14] A total of 1000 μg of each compound was added in sterile luke warm potato dextrose agar medium before pouring. Fungal agar plug of 5-day-old test culture was placed at the center of the medium plate. Plates were incubated at 28 °C for 7 days. Percentage inhibition of fungal culture in the presence of test compounds was assessed by comparing mycelia growth diameter on poisoned (media + compound) and nonpoisoned (media + DMSO) plates and calculated using the formula

$$\%\text{age inhibition} = [(R1 - R2)/R1] \times 100$$

R1 means radial growth of test fungi in nonpoisoned plate; R2 means radial growth of same in poisoned plate.

General procedure for the synthesis of 8(i–xiv) and 9(i–xiv)

A mixture of aldehyde (**5i–5xiv**, 1 mmol) and semicarbazide hydrochloride **6(i)** (0.11 g, 1 mmol)/thiosemicarbazide **6(ii)** (0.09 g, 1 mmol) in 1,4-dioxane (10 mL) was refluxed for the time mentioned in Scheme 2 to achieve the complete formation of the desired semicarbazones/thiosemicarbazones (TLC). At this stage, ninhydrin (0.21 g, 1.2 mmol) was added to the reaction mixture and refluxing was continued till the completion of reaction (time given in Scheme 2). The reaction mixture was poured into ice-cold water (50 mL) and kept in refrigerator overnight. The solid separated was filtered, dried, and column chromatographed to obtain the pure product [**8(i–xiv)**; **9(i–xiv)**; 78–93% yield].

Spectral characterization of (8i) and (9i)

3-(Benzylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **(8i)**; white solid; mp: 185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (bs, 2H), 7.98–7.77 (m, 3H), 7.72–7.63 (m, 4H), 7.53–7.34 (m, 3H), 7.05 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.5, 152.6, 151.6, 145.7, 137.7, 135.5, 132.1, 131.1, 130.1,

129. 2, 127.1, 125.5, 124.2, 89.8, 84.5; IR (KBr) ν_{max}/cm^{-1}: 3365.78, 1724.36, 1695.48; Anal. calcd. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00; found C, 63.12; H, 4.07; N, 12.96; ESI-MS *m/z*: $[M+H]^+ = 324$.

3-(Benzylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*] imidazol-8(2*H*)-one **(9i)**; yellow crystalline solid; mp: 203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (bs, 1H), 9.58 (s, 1H), 8.14–8.07 (d, $J = 8$ Hz, 1H), 7.97–7.86 (m, 4H), 7.79–7.69 (d, $J = 8.0$ Hz, 2H), 7.55 (s, 3H), 7.40 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.1, 174.9, 156.1, 148.4, 137.3, 134.4, 133.2, 131.5, 131.4, 129.4, 128.1, 127.4, 124.3, 92.7, 86.8; IR (KBr) ν_{max}/cm^{-1}: 3365.32, 1711.14, 1707.34, 1285.10; Anal. calcd. for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38; S, 9.45; found C, 60.01; H, 3.69; N, 12.84; S, 9.61; ESI-MS *m/z*: $[M+H]^+ = 340$.

Conclusion

A series of novel 3-(arylideneamino)-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*] imidazole-2,8-diones and 3-(arylideneamino)-3a,8a-dihydroxy-2-thioxo-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazol-8(2*H*)-ones have been synthesized through one-pot, catalyst-free reaction of aldehydes, semicarbazide hydrochloride/thiosemicarbazide with ninhydrin and screened for antimicrobial activity. Some of the synthesized compounds showed promising results.

Funding

The authors are grateful to DST for NMR facility under PURSE and UGC, New Delhi for funding (Project No. MRP-MAJOR-CHEM-2013-21745).

References

[1] Banerjee, S.; Mondal, S.; Chakraborty, W.; Sem, S.; Gachhui, R.; Butcher, R. J.; Slawin, A. M.; Mandal, C.; Mitra, S. Z. *Polyhedron* **2009**, *28*, 2785.

[2] (a) Despaigne, A. A. R.; Parrilha, G. L.; Izidoro, J. B.; da Costa, P. R.; dos Santos, R. G.; Piro, O. E.; Castellano, E. E.; Rocha, W. R.; Beraldo, H. *Eur. J. Med. Chem.* **2012**, *50*, 163 (b) Dandawate, P.; Khan, E.; Padhye, S.; Gaba, H.; Sinha, S.; Deshpande, J.; Swamy, K. V.; Khetmalas, M.; Ahmad, A.; Sarkar, F. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3104; (c) Mohareb, R. M.; Al-Omran, F. *Steroids* **2012**, *77*, 1551; (d) Aydin, S.; Kaushik Basu, N.; Arora, P.; Basu, A.; Nichols, B. D.; Talele, T. T.; Akkurt, M.; Celik, I.; Buyukgungor, O.; Kucukguzel, S. G. *Marmara Pharm. J.* **2013**, *17*, 26.

[3] (a) Fattorusso, C.; Campiani, G.; Kukreja, G.; Persico, M.; Butini, S.; Romano, M. P.; Altarelli, M.; Ros, S.; Brindisi, M.; Savini, L.; Novellino, E.; Nacci, V.; Fattorusso, E.; Parapini, S.; Basilico, N.; Taramelli, D.; Yardley, V.; Croft, S.; Borriello, M.; Gemma, S. *J. Med. Chem.* **2008**, *51*, 1333; (b) Acharya, B. N.; Saraswat, D.; Kaushik, M. P. *Eur. J. Med. Chem.* **2008**, *43*, 2840.

[4] (a) El-Sabbagh, O. L.; Rady, H. M. *Eur. J. Med. Chem.* **2009**, *44*, 3680 (b) Tian, B.; He, M.; Tang, S.; Hewlett, I.; Tan, Z.; Li, J.; Jin, Y.; Yang, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2162.

[5] (a) Secci, D.; Bizzarri, B.; Bolasco, A.; Carradori, S.; D' Ascenzio, M.; Rivanera, D.; Mari, E.; Polletta, L.; Zicari, A. *Eur. J. Med. Chem.* **2012**, *53*, 246; (b) Maillard, L. T.; Bertout, S.; Quinonera, O.; Akalin, G.; Turan-Zitouni, G.; Fulcrand, P.; Demirci, F.; Martinez, J.; Masurier, N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1803; (c) Altintop, M. D.; Ozdemir, A.; Turan Zitouni, G.; llgin, S.; Atli, O.; lscan, G.; Kaplancikli, Z. A. *Eur. J. Med. Chem.* **2012**, *58*, 299;

(d) Kocyigit-Kaymakcioglu, B.; Oruc-Emre, E. E.; Unsalan, S.; Tabanca, N.; Khan, S. I.; Wedge, D. E.; Iscan, G.; Demirci, F.; Rollas, S. *Med. Chem. Res.* **2012**, *21*, 3499.

[6] (a) Abdel-Aziz, H. A.; Mekawey, A. A. *Eur. J. Med. Chem.* **2009**, *44*, 4985; (b) Abdel-Wahab, B. F.; Awad, G. E.; Badria, F. A. *Eur. J. Med. Chem.* **2011**, *46*, 1505; (c) Khan, S. A. *Eur. J. Med. Chem.* **2008**, *43*, 2040.

[7] (a) Telvekar, V. N.; Belubbi, A.; Bairwa, V. K.; Satardekar, K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2343; (b) Gemma, S.; Savini, L.; Altarelli, M.; Tripaldi, P.; Chiasserini, L.; Coccone, S. S.; Kumar, V.; Camodeca, C.; Campiani, G.; Novellino, E.; Clarizio, S.; Delogu, G.; Butini, S.; *Bioorg. Med. Chem.* **2009**, *17*, 6063; (c) Imramovsky, A.; Polanc, S.; Vinsova, J.; Kocevar, M.; Jampilek, J.; Reckova, Z. *Bioorg. Med. Chem.* **2007**, *15*, 2551.

[8] (a) Gokce, M.; Utku, S.; Kupeli, E. *Eur. J. Med. Chem.* **2009**, *44*, 3760; (b) Khan, K. M.; Khan, M.; Ali, M.; Taha, M.; Rasheed, S.; Perveen, S.; Choudhary, M. I. *Bioorg. Med. Chem.* **2009**, *17*, 7795; (c) Moldovan, C. M.; Oniga, O.; Parvu, A.; Tiperciuc, B.; Verite, P.; Pirnau, A.; Crisan, O.; Bojita, M.; Pop, R. *Eur. J. Med. Chem.* **2011**, *46*, 526.

[9] (a) Alizadeh, A.; Zarei, A.; Rezvanian, A. *Helv. Chim. Acta* **2011**, *94*, 802; (b) Das, S.; Frohlich, R.; Pramanik, A. *Org. Lett.* **2006**, *8*, 426; (c) Seyfi, S.; Hossaini, Z.; Rostami-Charati, F. *Comb. Chem. High Throughput Screen.* **2013**, *16*, 652.

[10] Ghalib, R. M.; Hashim, R.; Alshahateet, S. F.; Mehdi, S. H.; Sulaiman, O.; Murugaiyah, V.; Aruldass, C. A. *J. Mol. Struct.* **2011**, *1005*, 152.

[11] Ghalib, R. M.; Hashim, R.; Alshahateet, S. F.; Mehdi, S. H.; Sulaiman, O.; Chan, K.-L.; Murugaiyah, V.; Jawad, A. J. *Chem. Crystallogr.* **2012**, *42*, 783.

[12] (a) Chang, S.-J.; McNally, D.; Shary-Tehrany, S.; Hickey, S. M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109; (b) Kim, W.-Y.; Kim, B. G.; Kang, T.; Lee, H.-Y. *Chem. Asian J.* **2011**, *6*, 1931.

[13] Rahman, A.-U.; Choudhary, M. I.; Thomsen, W. J. *In Bioassay Techniques for Drug Development*; Harwood Academic Publishers: The Netherlands, 2001; 16.

[14] Das, K.; Tiwari, R. K. S.; Shrivastava, D. K. *J. Med. Plants Res.* **2010**, *4*, 104–111.

Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 1330

Iodine–NH_4OAc mediated regioselective synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines from 1,3-diaryl-prop-2-en-1-ones†

Dilpreet Kour,[a] Annah Gupta,[a] Kamal K. Kapoor,*[a] Vivek K. Gupta,[b] Rajnikant,[b] Deepika Singh[c] and Parthasarathi Das *‡[c]

Received 9th November 2017,
Accepted 22nd January 2018

DOI: 10.1039/c7ob02750h

rsc.li/obc

The present protocol describes an efficient, metal-free regioselective synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines from 1,3-diaryl-prop-2-en-1-ones and 2-aminopyridine. The iodine–NH_4OAc promoted reaction offers a novel route in the synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines. This protocol offers significant flexibility in accessing medicinally important 2-aroyl-3-arylimidazo[1,2-*a*]pyridines with various substitution patterns.

Introduction

Imidazo[1,2-*a*]pyridines are aza-fused heterocyclic compounds widely distributed in many pharmacologically important compounds.[1] In addition, these nitrogen-bridgehead fused heterocycles are also known to possess applications in the field of materials and organometallic chemistry.[2] These derivatives exhibit a broad spectrum of biological activities[3] such as anti-cancer,[4] anti-viral,[5] anti-inflammatory,[6] anti-pyretic,[7] anti-ulcer[8] and anti-bacterial.[9] It is pertinent to mention that 6-chloro-2-ethyl-*N*-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl)imidazo(1,2-*a*)pyridine-3-carboxamide (Q203) has successfully completed phase-I studies for the treatment of multidrug resistant strains of *Mycobacterium tuberculosis*[10] (Fig. 1). Many drugs featuring the imidazo[1,2-*a*]pyridine scaffold are commercially available in the market and are shown in Fig. 1. Furthermore, imidazo[1,2-*a*]pyridine also finds application in the field of optoelectronics *e.g.* 2-(2-hydroxy phenyl)imidazo[1,2-*a*]pyridines exhibit excellent excited state intramolecular proton transfer (ESIPT).[11] Owing to its extensive range of bioactivities, the importance of the imidazo[1,2-*a*]pyridine scaffold in the pharmaceutical sector is well appreciated among the chemists and this has led a surge in the development of newer efficient and facile methods for its synthesis.

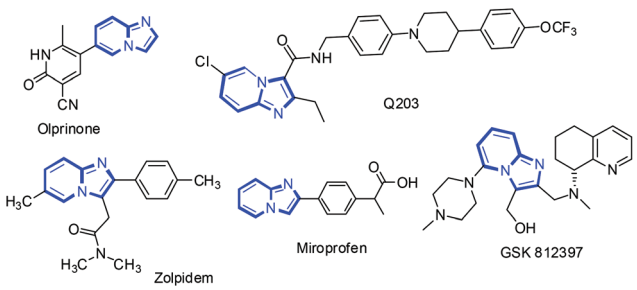


Fig. 1 Biologically active imidazo[1,2-*a*]pyridines.

Various analogues of imidazopyridine have been synthesized[12] and among them, aroylimidazo[1,2-*a*]pyridines have emerged as the interesting structures since aroyl functionality has been found to be responsible for their elevated biological properties.[3,13]Nowadays, emphasis is on the development of metal-free synthetic protocols. In this perspective, molecular iodine has proven to be an efficient mediator in the synthesis of various heterocycles[14] due to its role in oxidative coupling reactions for the construction of C–C,[15] C–N[16] and C–X[17] bonds. Iodine-mediated reactions have been extensively encouraged in the synthesis of various natural products and biologically active scaffolds since they are non-toxic, readily available, inexpensive Lewis acids compared to transition metal catalysts and are easy to handle.[18] Moreover, iodine-promoted reactions generally involve domino reaction sequences and forms several bonds in a single operation.[19]

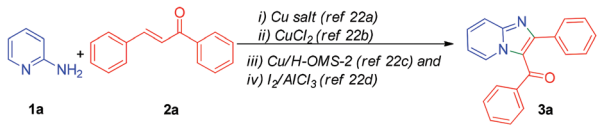
Imidazopyridines with diverse substitution patterns have mainly been synthesized from 2-aminopyridine[20] and the mode of first nucleophilic attack by either *exo* amine[21,22] or

[a]*Department of Chemistry, University of Jammu, Jammu-180006, India. E-mail: k2kapoor@yahoo.com*
[b]*X-ray Crystallographic Group, Department of Physics, University of Jammu, Jammu-180006, India*
[c]*Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu-180001, India*

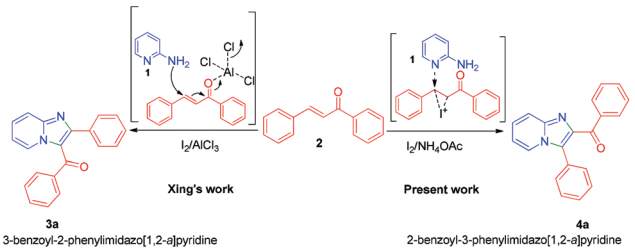
†Electronic supplementary information (ESI) available. CCDC 1538920. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob02750h

‡Current address: Department of Applied Chemistry, Indian Institute of Technology (ISM), Dhanbad 826004, India. E-mail: partha@iitism.ac.in

Previous reports for the synthesis of 3-benzoyl-2-phenyl imidazo[1,2-*a*]pyridine



Origin of the present work



Scheme 1 Synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines.

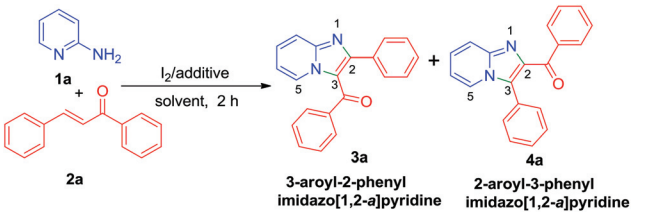
endo nitrogen[23] dictates their regiochemical outcome. When 2-aminopyridine reacts with 1,3-diaryl-prop-2-en-1-one, two different types of regioisomers **3** and **4** are observed and surprisingly, all the literature reports, till date, have described the formation of 3-aroyl-2-arylimidazo[1,2-*a*]pyridines **3** (Scheme 1).[22]

In order to prepare 2-aroyl-3-arylimidazo[1,2-*a*]pyridines **4**, we decided to use I_2 as a reagent that might lead to the formation of a 3-membered iodonium complex,[24] thereby providing the necessary impetus for the attack by the *endo* nitrogen of 2-aminopyridine to occur at the β-carbon akin to Ortoleva–King reactions.[23h,25,26]

Results and discussion

To optimize the reaction conditions, we commenced our study by reacting 2-aminopyridine **1a** and 1,3-diphenyl-prop-2-en-1-one **2a** as the model substrates. The initial reaction was carried out by refluxing a mixture of 2-aminopyridine **1a** (1.2 mmol), 1,3-diphenyl-prop-2-en-1-one **2a** (1.0 mmol) and I_2 (1.0 mmol) in $CHCl_3$ (entry 1, Table 1) and to our delight, product **4a** was isolated in 60% yield. Unlike 3-aroyl-2-phenylimidazo[1,2-*a*]pyridine **3a**, a doublet at δ 9.55 diagnostic for the C-5 proton was missing in ^{1}H NMR of product **4a**. A scrutiny of the spectral data (^{1}H NMR, ^{13}C NMR, and HRMS) confirms the structure of **4a** as 2-aroyl-3-phenylimidazo[1,2-*a*]pyridine *i.e.* the regiomer of **3a**. The downfield appearance of C_5–H in **3a** is due to the anisotropy of the carbonyl of the 3-aroyl moiety which is absent in **4a**. The proposed structure of the present methodology was further corroborated by the single X-ray diffraction analysis of the compound **4d** (Table 2). Investigation revealed that $CHCl_3$ (entry 1, Table 1) was the most suitable among the various solvents (DCE, CH_3CN, DMF, EtOH, 1,4-dioxane, toluene and chlorobenzene) screened (Table 1). Based

Table 1 Optimization of the reaction conditions[a]



Entry	Additive	Solvent	Yield[b] (%) **3a**/**4a**
1	—	$CHCl_3$	00/60
2	—	DCE	00/30
3	—	EtOH	00/43
4	—	Toluene	00/30
5	—	CH_3CN	00/37
6	—	DMF	00/15
7	—	1,4-Dioxane	00/21
8	—	Chlorobenzene	00/55
9	NH_4OAc	$CHCl_3$	00/85
10[c]	NH_4OAc	$CHCl_3$	00/70
11[d]	NH_4OAc	$CHCl_3$	00/82
12	NH_4Cl	$CHCl_3$	00/40
13	$(NH_4)_2SO_4$	$CHCl_3$	00/33
14[e]	DABCO	$CHCl_3$	10/17
15[e]	DBU	$CHCl_3$	20/20
16[e]	*p*-TsOH	$CHCl_3$	20/40
17	NaOAc	$CHCl_3$	00/30
18[f]	NH_4OAc	$CHCl_3$	00/55
19[g]	—	$CHCl_3$	ND/ND

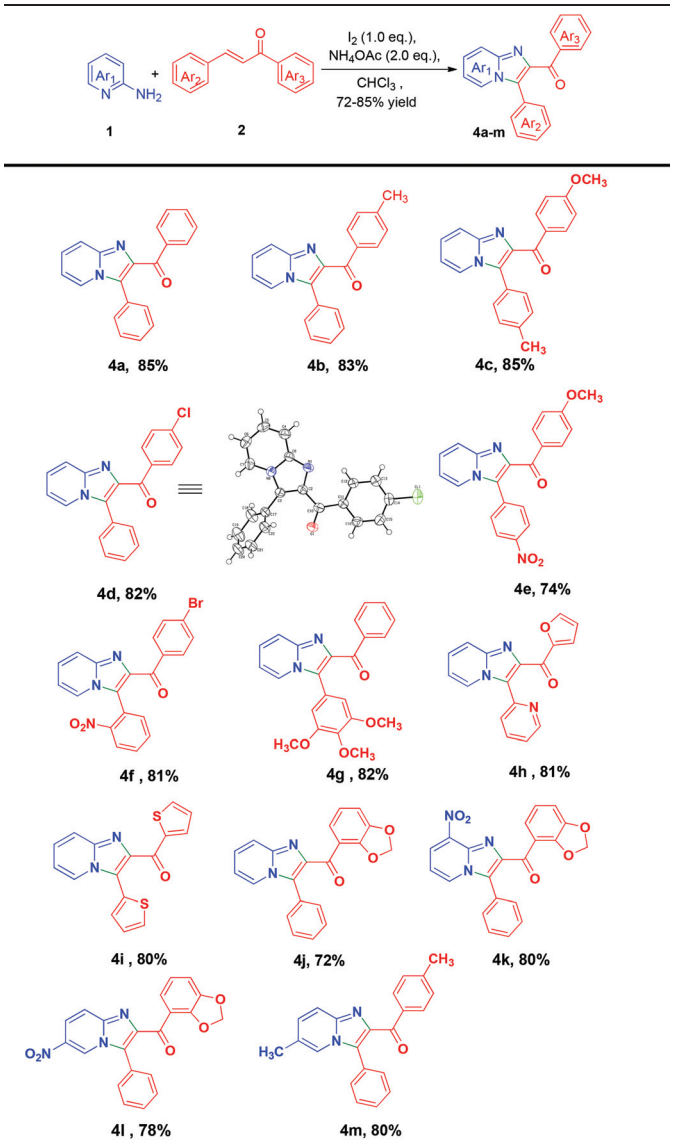
[a] Reaction conditions: **1a** (1.2 equiv.), **2a** (1.0 equiv.), I_2 (1.0 equiv.), NH_4OAc (2.0 equiv.), $CHCl_3$ (10 mL), reflux, 2 h. [b] Isolated yields. [c] (1.0 equiv.). [d] (3.0 equiv.). [e] Reaction run for 20 h. [f] In the presence of NIS. [g] In the absence of I_2, ND = not detected.

on our previous experience, we decided to use NH_4OAc to increase the yield of the product.[26] To our delight, a good improvement in the yield of the product **4a** was noticed upon the addition of 2 equiv. of NH_4OAc (entry 9, Table 1).

However, the use of different amounts of NH_4OAc (entries 9–11, Table 1) revealed that the optimum requirement of the reaction is 1 equiv. of I_2 and 2 equiv. of NH_4OAc with respect to 1,3-diaryl-prop-2-en-1-one (entry 9, Table 1). Other additives such as NH_4Cl, $(NH_4)_2SO_4$, DABCO, DBU, *p*-TsOH and NaOAc did not result in any improvement in the yield (entries 12–17, Table 1). But when DABCO, DBU and *p*-TsOH were used, the formation of a mixture of **3a** and **4a** was observed (entries 14–16, Table 1). It is noteworthy to mention here that the formation of the desired product **4a** did not occur in the absence of I_2 (entry 19, Table 1).

After having the optimized reaction conditions in hand, we became interested in exploring the substrate scope by reacting various substituted 2-aminopyridines and 1,3-diphenyl-prop-2-en-1-ones and the results are shown in Table 2. Various 1,3-diaryl-prop-2-en-1-ones bearing electron-donating groups (Me, OMe, oxymethylene), electron-withdrawing groups (NO_2) and halo-derivatives (Cl, Br) reacted efficiently giving the corresponding 2-aroyl-3-arylimidazo[1,2-*a*]pyridines in very good yields (72–85%). Heteryl ring systems (**4h–i**, Table 2) were also well tolerated under the present reaction conditions. The

Table 2 Synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines[a,b]

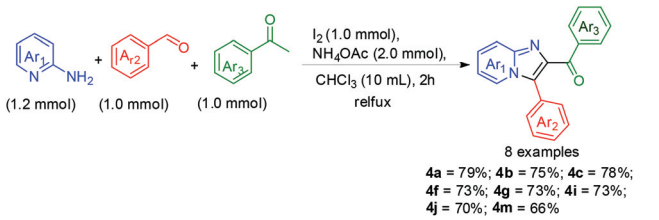


[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), iodine (1 mmol), NH_4OAc, (2.0 mmol), $CHCl_3$ (10 mL), reflux. [b] Isolated yields.

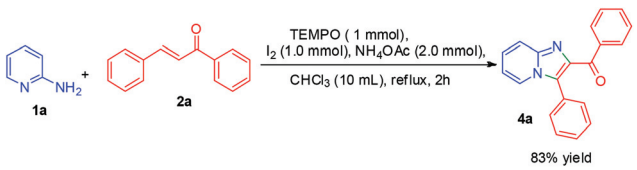
present method also works well both with electron-donating and electron-withdrawing 2-aminopyridines (**4k–m**, Table 2).

Furthermore, to make this approach more expedient, a one-pot synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines was also investigated and this includes the heating of aryl methyl ketones, aryl/heteroaldehydes and 2-aminopyridine in the presence of I_2 and NH_4OAc in $CHCl_3$ (Scheme 2). The reaction proceeded *via in situ* formation of 1,3-diaryl-prop-2-en-1-ones and this is supported by the mass spectrum of the aliquot taken after four minutes of the reaction. However, the yield of the reaction was observed to be slightly less than the one reported with a 2-component reaction (Table 2).

The addition of 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) had no significant impact on the yield of the product



Scheme 2 One-pot synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines.

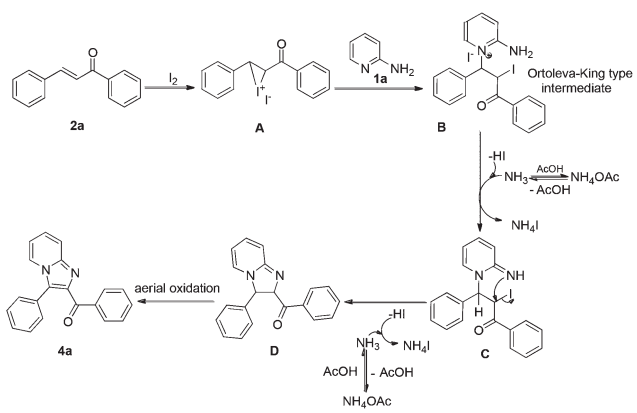


Scheme 3 Control experiment.

which suggested the formation of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines through a non-radical pathway (Scheme 3). The reaction that was also tested with another source of the iodonium ion such as NIS (1 eq.) (Table 1, entry 18) gave only one product **4a** (55% yield) supporting the iodonium intermediate.

On the basis of these results, a plausible mechanism for the synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines **4a–m** is illustrated in Scheme 4. In the first step, iodine reacts with 1,3-diaryl-prop-2-ene-1-one (**2a**) to form iodonium intermediate **A**.[24] Then, C–N bond formation occurs by the attack of endocyclic pyridine nitrogen of 2-aminopyridine on the β-position of the iodonium intermediate[27] forming intermediate **C** *via* Ortoleva–King type intermediate[23h,25,26] **B**. Next, the intramolecular cyclization of intermediate **C** leads to the formation of intermediate **D** which undergoes aerial oxidation to form the desired product **4a**. HI produced during the reaction is believed to be scavenged by NH_3 produced from NH_4OAc.[26]

To support the proposed mechanism, mass spectra of the aliquot taken out at different time intervals were recorded on a Waters Quattro Premier Triple Quad instrument in positive ion



Scheme 4 Plausible reaction mechanism.

Table 3 Mass spectrum of the reaction mixture at different time intervals[a]

Entry	**2a** (208)	**A** (334)	**B** (429)	**C** (428)	**D** (300)	**4a** (298)
2 min	✓	✓	✓	✓	✓	✓
10 min	✓	✓	ND	✓	✓	✓
55 min	✓	ND	ND	ND	ND	✓

[a] Reaction conditions: **1a** (1.2 equiv.), **2a** (1.0 equiv.), I_2 (1.0 equiv.), NH_4OAc (2.0 equiv.), $CHCl_3$ (10 mL), reflux, ✓ = detected, ND = not detected.

mode (Table 3). As is evident from the table, the aliquot taken after 2 minutes of the reaction displayed masses corresponding to starting material **2a**, intermediates **A**, **B**, **C** and **D**, and the product **4a**. In 10 minutes, a mass peak corresponding to Ortoleva–King intermediate **B** was found missing revealing the consumption of the product. Furthermore, after 55 minutes, the aliquot showed the presence of only the product **4a** with the disappearance of all the intermediates (see the ESI† for details).

Conclusions

In conclusion, a direct regioselective synthesis of pharmaceutically important 2-functionalised imidazopyridine derivatives has been reported from 2-aminopyridine and 1,3-diaryl-prop-2-en-1-ones. This metal-free, one-pot protocol is simple, facile and offers a significant flexibility to access an array of fused 2-aroyl-3-arylimidazo[1,2-*a*]pyridines. This synthetic route definitely opens-up the possibilities of synthesizing the new pharmacologically important imidazopyridine scaffolds. The one-pot three-component synthesis of 2-aroyl-3-arylimidazo [1,2-*a*]pyridines has also been reported from aryl methyl ketones, aryl/heteraldehydes and 2-aminopyridine under similar reaction conditions. The dual C–N bond formations with high regioselectivity, utilizing readily available precursors, are the notable advantageous features of the present protocol.

Experimental

All the commercially available reagents were purchased from Aldrich and were used without further purification. Melting points (°C) were measured in open glass capillaries using a Perfit melting-point apparatus and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica-gel pre-coated aluminium sheets (60 F254, Merck). The visualization of spots was effected by exposure to ultraviolet light (UV) at 254 nm and iodine vapours, and by treating the plates with Dragendorff's reagent followed by heating. Column chromatography was performed on silica gel (60–120 mesh). ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ as the solvent were recorded on a Bruker AC-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, with tetramethylsilane (TMS) as an internal standard. For HRMS measurements, Q-TOF was used.

Experimental procedure for the synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines (4a–m)

A mixture of 2-aminopyridine (1.2 mmol), 1,3-diaryl-prop-2-en-1-one (1.0 mmol), iodine (1.0 mmol) and NH_4OAc (2.0 mmol) was taken in a 100 mL round-bottomed flask and was refluxed in $CHCl_3$ (10 mL) until the completion of the reaction as observed by TLC. The reaction mixture was further diluted with 20 mL of $CHCl_3$, washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), water (1 × 10 mL) and brine (1 × 10 mL), and finally dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The desired product was obtained after column chromatography.

General procedure for an I_2/NH_4OAc-mediated one-pot reaction for the synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridines

A mixture of 2-aminopyridine (1.2 mmol), aryl methyl ketone (1.0 mmol), aryl/heteroaldehyde (1.0 mmol), iodine (1 mmol) and NH_4OAc (2 mmol) was taken in a 100 mL round-bottomed flask and was refluxed in $CHCl_3$ (10 mL) until the completion of the reaction as observed by TLC. The reaction mixture was further diluted with 20 mL of $CHCl_3$, washed with a saturated solution of $Na_2S_2O_3$ (2 × 10 mL), water (1 × 10 mL) and brine (1 × 10 mL), and finally dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The desired product was obtained after column chromatography.

Phenyl(3-phenylimidazo[1,2-*a*]pyridin-2-yl)methanone (4a)

White solid (253 mg, 85%); mp: 108–110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.21 (d, J = 7.6 Hz, 2H), 8.06 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.58–7.45 (m, 8H), 7.34–7.30 (m, 1H), 6.89 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 190.0, 143.9, 140.2, 137.6, 135.3, 132.7, 131.7, 130.8, 129.3, 128.1, 127.7, 126.7, 126.1, 123.7, 119.2, 114.0; IR (KBr) (ν_{max}, cm^{-1}): 3077.56, 2924.21, 1648.24, 1358.91, 1252.82; HRMS (ESI): calcd for $C_{20}H_{15}N_2O$ $(M + H)^+$, 299.1176; found: 299.1181.

(3-Phenylimidazo[1,2-*a*]pyridin-2-yl)(*p*-tolyl)methanone (4b)

Oil (258 mg, 83%); ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.12–8.08 (m, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.57–7.47 (m, 5H), 7.33–7.24 (m, 4H), 6.88–6.84 (m, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 189.9, 144.4, 143.8, 143.7, 143.3, 140.3, 135.6, 134.9, 130.9, 130.4, 130.3, 129.3, 129.1, 128.9, 128.8, 128.6, 128.4, 128.3, 125.9, 124.0, 122.0, 119.0, 113.7, 21.7; IR (KBr) (ν_{max}, cm^{-1}): 3067.12, 1645.00, 1498.00, 1251.29; HRMS (ESI): calcd for $C_{21}H_{17}N_2O$ $(M + H)^+$, 313.1333; found: 313.1339.

(4-Methoxyphenyl)(3-(*p*-tolyl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4c)

Light yellow solid (290 mg, 85%); mp: 124–126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27–8.24 (m, 2H), 8.11 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.34–7.27 (m, 3H), 6.97–6.93 (m, 2H), 6.86–6.82 (m, 1H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.7, 163.2, 143.6, 140.3,

139.1, 133.2, 132.0, 130.7, 130.2, 129.7, 128.7, 125.7, 125.3, 124.0, 118.9, 113.4, 113.3, 55.4, 21.4; IR (KBr) (ν_{max}, cm^{-1}): 3056.00, 1645.49, 1490.0, 1250.80; HRMS (ESI): calcd for $C_{22}H_{19}N_2O_2$ $(M + H)^+$, 343.1438; found: 343.1433.

(4-Chlorophenyl)(3-phenylimidazo[1,2-*a*]pyridin-2-yl) methanone (4d)

Shiny brown crystal (272 mg, yield 82%); mp: 147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 6.8 Hz, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.56–7.51 (m, 5H), 7.43 (d, J = 8.4 Hz, 2H), 7.34–7.30 (m, 1H), 6.88 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.8, 143.9, 139.6, 138.9, 136.1, 132.2, 130.3, 129.3, 129.0, 128.3, 128.1, 126.2, 124.0, 119.1, 113.8; IR (KBr) (ν_{max}, cm^{-1}): 3068.11, 16 344.00, 1486.90, 1265.00; HRMS (ESI): calcd for $C_{20}H_{14}ClN_2O$ $(M + H)^+$, 333.0786; found: 333.0779.

(4-Methoxyphenyl)(3-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4e)

Oil (276 mg, 74%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J = 8.4 Hz, 2H), 8.30 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 7.2 Hz, 1H), 7.80 [d, J = 8.4 Hz, 3H (2H + 1H)], 7.40–7.36 (m, 1H), 7.00–6.94 (m, 3H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2, 163.6, 144.4, 141.6, 139.8, 135.3, 133.3, 131.3, 130.2, 130.0, 126.5, 124.1, 123.4, 119.4, 114.4, 113.6, 55.5; IR (KBr) (ν_{max}, cm^{-1}): 2931.93, 1599.06, 1513.22, 1339.62, 1260.54; HRMS (ESI): calcd for $C_{21}H_{16}N_3O_4$: $(M + H)^+$, 374.1133; found: 374.1141.

(4-Bromophenyl)(3-(2-nitrophenyl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4f)

Crystalline brown solid (341 mg, 81%); mp: 135–139 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.83–7.73 (m, 4H), 7.65–7.61 (m, 2H), 7.58 (dd, J = 7.6, 1.2 Hz, 1H), 7.40–7.36 (m, 1H), 6.91 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2, 149.5, 144.3, 139.9, 136.1, 133.6, 133.4, 132.4, 132.0, 131.4, 130.8, 129.5, 128.0, 126.4, 125.2, 125.0, 124.0, 123.9, 119.3, 114.3; IR (KBr) (ν_{max}, cm^{-1}): 3104.56, 1634.74, 1524.79, 1242.21; HRMS (ESI): calcd for $C_{20}H_{13}BrN_3O_3$: $(M + H)^+$, 422.0132; found: 422.0143.

Phenyl(3-(3,4,5-trimethoxyphenyl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4g)

Off-white solid (318 mg, 82%); mp: 105–107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 [d, J = 7.2 Hz, 3H (2H + 1H)], 7.73 (d, J = 9.2 Hz, 1H), 7.53–7.50 (m, 1H), 7.44–7.40 (m, 2H), 7.31–7.28 (m, 1H), 6.87 (t, J = 6.8 Hz, 1H), 6.74 (s, 2H), 3.90 (s, 3H), 3.84 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.4, 153.6, 143.8, 139.8, 138.7, 137.8, 132.5, 130.6, 129.4, 128.8, 128.0, 127.8, 126.0, 124.2, 123.4, 119.0, 113.7, 107.6, 60.9, 56.3, 55.9; IR (KBr) (ν_{max}, cm^{-1}): 3085.00, 1624.76, 1489.00, 1238.13; HRMS (ESI): calcd for $C_{23}H_{21}N_2O_4$: $(M + H)^+$, 389.1493; found: 389.1499.

Furan-2-yl(3-(pyridin-2-yl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4h)

Viscous oil (234 mg, 81%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70–8.63 (m, 2H), 8.13 (d, J = 8.0 Hz, 1H), 7.88 (dt, J = 7.7, 1.7 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.58 (brs, 1H), 7.46–7.42 (m, 1H), 7.35–7.30 (m, 1H), 7.17 (d, J = 3.2 Hz, 1H), 6.96–6.92 (m, 1H), 6.56–6.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.5, 155.1, 149.1, 144.5, 143.1, 142.7, 140.0, 136.6, 126.5, 126.1, 126.0, 124.8, 120.3, 119.2, 114.1, 113.4, 111.7; IR (KBr) (ν_{max}, cm^{-1}): 3074.28, 1634.69, 1482.99, 1276.00; HRMS (ESI): calcd for $C_{17}H_{12}N_3O_2$: $(M + H)^+$, 290.0921; found: 290.0925.

Thiophen-2-yl(3-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-2-yl) methanone (4i)

Yellow crystals (248 mg, 80%); mp: 160–162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, J = 3.6 Hz, 1H), 8.19 (d, J = 7.2 Hz, 1H), 7.73–7.69 (m, 2H), 7.57 (d, J = 5.2 Hz, 1H), 7.41 (d, J = 3.6 Hz, 1H), 7.32–7.30 (m, 1H), 7.23–7.20 (m, 1H), 7.18–7.16 (m, 1H), 6.87 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.6, 144.2, 143.4, 140.8, 136.1, 134.7, 130.4, 128.6, 127.9, 127.8, 127.4, 126.5, 124.5, 121.6, 118.9, 114.0; IR (KBr) (ν_{max}, cm^{-1}): 3089.00, 16 290.72, 1483.90, 1243.21; HRMS (ESI): calcd for $C_{16}H_{11}N_2OS_2$: $(M + H)^+$, 311.0305; found: 311.0305.

Benzo[*d*][1,3]dioxol-4-yl(3-phenylimidazo[1,2-*a*]pyridin-2-yl) methanone (4j)

Yellow oil (246 mg, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.76–7.72 (m, 2H), 7.57–7.48 (m, 5H), 7.33–7.28 (m, 1H), 6.89–6.84 (m, 2H), 6.04 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2, 151.5, 147.5, 143.7, 140.3, 132.3, 130.3, 130.1, 129.1, 128.9, 128.6, 128.3, 127.7, 125.9, 123.9, 119.0, 113.6, 110.5, 107.7, 101.6; IR (KBr) (ν_{max}, cm^{-1}): 3074.98, 1629.00, 1498.00, 1256.80; HRMS (ESI): calcd for $C_{21}H_{15}N_2O_3$: $(M + H)^+$, 343.1074; found: 343.1070.

Benzo[*d*][1,3]dioxol-4-yl(8-nitro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)methanone (4k)

Dark brown solid (309 mg, 80%); mp: 216–218 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (brs, 1H), 8.09–8.06 (m, 1H), 7.90 (dd, J = 8.0, 1.6 Hz, 1H), 7.83 (d, J = 9.8 Hz, 1H), 7.69 (brs, 1H), 7.60–7.56 (m, 5H), 6.88 (d, J = 8.4 Hz, 1H), 6.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.1, 152.0, 147.8, 143.4, 143.1, 138.3, 131.6, 130.9, 130.2, 130.2, 129.4, 127.9, 126.5, 124.5, 119.9, 118.8, 110.2, 107.8, 101.8; IR (KBr) (ν_{max}, cm^{-1}): 3118.06, 2913.60, 1632.81, 1481.39, 1250.89; HRMS (ESI): calcd for $C_{21}H_{14}N_3O_5$: $(M + H)^+$, 388.0925; found: 388.0930.

Benzo[*d*][1,3]dioxol-4-yl(6-nitro-3-phenylimidazo[1,2-*a*]pyridin-2-yl)methanone (4l)

Light green solid (301 mg, 78%); mp: 279–281 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (s, 1H), 8.08 (d, J = 9.6 Hz, 1H), 7.90–7.82 (m, 2H), 7.69–7.58 (m, 6H), 6.89 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz,): δ 187.0, 152.0, 147.8, 143.4, 143.1, 138.3, 131.6, 130.8, 130.2, 130.2 129.4, 127.9, 126.5, 124.5, 119.9, 118.8, 110.2, 107.8, 101.8; IR (KBr) (ν_{max}, cm^{-1}): 3073.34, 2900.43, 1618.28, 1491.65, 1248.37; HRMS (ESI): calcd for $C_{21}H_{14}N_3O_5$: $(M + H)^+$, 388.0925; found: 388.0931.

(6-Methyl-3-phenylimidazo[1,2-*a*]pyridin-2-yl)(*p*-tolyl) methanone (4m)

White solid (260 mg, yield 80%); mp: 155–160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, J = 8.0 Hz, 2H), 7.85 (s, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.56–7.47 (m, 5H), 7.24 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 9.2 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz,): δ 189.9, 143.1, 142.9, 140.3, 135.4, 130.8, 130.4, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 123.4, 121.2, 118.3, 21.6, 18.4; IR (KBr) (ν_{max}, cm^{-1}): 3073.16, 1623.72, 1490.24, 1256.49; HRMS (ESI): calcd for $C_{22}H_{19}N_2O$ $(M + H)^+$, 327.1489; found: 327.1496.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful to the Department of Chemistry, University of Jammu, for providing all necessary facilities and the Department of Science and Technology, Government of India, New Delhi, for NMR facility under PURSE and INSPIRE fellowships [AG]. This research work is financially supported by University Grants Commission, New Delhi (Project No. MRP-MAJOR-CHEM-2013-21745).

Notes and references

1 For selected articles, see: (*a*) A. C. Humphries, E. Gancia, M. T. Gilligan, S. Goodacre, D. Hallett, K. J. Marchant and S. R. Thomas, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1518; (*b*) M. A. Ismail, R. Brun, T. Wenzler, F. A. Tanious, W. D. Wilson and D. W. Boykin, *J. Med. Chem.*, 2004, **47**, 3658; (*c*) S. Ulloora, R. Shabaraya and A. V. Adhikari, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3368; (*d*) M. Hieke, C. B. Rodl, J. M. Wisniewska, E. Buscato, H. Stark, M. S. Zsilavecz, D. Steinhilber, B. Hofmann and E. Proschak, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1969.

2 (*a*) J. Wan, C. J. Zheng, M. K. Fung, X. K. Liu, C. S. Lee and X. H. Zhang, *J. Mater. Chem.*, 2012, **22**, 4502; (*b*) S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito and Y. Yamashita, *Chem. Lett.*, 2005, **34**, 1222; (*c*) S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito and Y. Yamashita, *Inorg. Chem.*, 2007, **46**, 4308; (*d*) A. John, M. M. Shaikh and P. Ghosh, *Dalton Trans.*, 2009, 10581; (*e*) G. Song, Y. Zhang and X. Li, *Organometallics*, 2008, **27**, 1936; (*f*) N. Chernyak and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 2743.

3 C. E. Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.*, 2007, **7**, 888.

4 C. Hamdouchi, J. D. Blas, D. Prado, J. Gruber, B. A. Heinz and L. Vance, *J. Med. Chem.*, 1999, **42**, 50.

5 A. Elkakmaoui, A. Gueiffier, J. C. Milhavet, Y. Blache, J. P. Chapat, O. Chavignon, J. C. Teulade, R. Snoeck, G. Andrei and E. D. Clerc, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1937.

6 R. B. Lacerda, C. K. F. de Lima, L. L. da Silva, N. C. Romeiro, A. L. P. Miranda, E. J. Barreiro and C. A. M. Fraga, *Bioorg. Med. Chem.*, 2009, **17**, 74.

7 L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem.*, 1965, **8**, 305; (*a*) T. Li, Z. Wang, K. Xu, W. Liu, X. Zhang, W. Mao, Y. Guo, X. Ge and F. Pan, *Org. Lett.*, 2016, **18**, 1064; (*b*) Y. Li, F. Xie and X. Li, *J. Org. Chem.*, 2016, **81**, 715.

8 J. J. Kaminski and A. M. Doweyko, *J. Med. Chem.*, 1997, **40**, 427.

9 K. F. Byth, J. D. Culshaw, S. Green, S. E. Oakes and A. P. Thomas, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2245.

10 (*a*) K. Pethe, P. Bifani, J. C. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Y. Jung, H. K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A. J. Lenaerts, H. Pham, V. Jones, M. J. Seo, Y. M. Kim, M. Seo, J. J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S. Y. Kim, S. Lim, S. A. Yim, J. Nam, H. Kang, H. Kwon, C. T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B. H. Tan, M. B. Nanjundappa, S. P. S. Rao, W. S. Barnes, R. Wintjens, J. R. Walker, S. Alonso, S. Lee, J. Kim, S. Oh, T. Oh, U. Nehrbass, S. J. Han, Z. No, J. Lee, P. Brodin, S. N. Cho, K. Nam and J. Kim, *Nat. Med.*, 2013, **19**, 1157; (*b*) https://clinicaltrials.gov/ct2/show/NCT00006150.

11 (*a*) A. Douhal, F. A. Guerri and A. U. Acuna, *J. Phys. Chem.*, 1995, **99**, 76; (*b*) A. Douhal, F. A. Guerri and A. U. Acuiia, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1514.

12 (*a*) S. Kang, R. Y. Kim, M. J. Seo, S. Lee, Y. M. Kim, M. Seo, J. J. Seo, Y. Ko, I. Choi, J. Jang, J. Nam, S. Park, H. Kang, H. J. Kim, J. Kim, S. Ahn, K. Pethe, K. Nam, Z. No and J. Kim, *J. Med. Chem.*, 2014, **57**, 5293; (*b*) N. Masurier, E. Debiton, A. Jacquemet, A. Bussiere, J. M. Chezal, A. Ollivier, D. Tetegan, M. Andaloussi, M. J. Galmier, J. Lacroix, D. Canitrot, J. C. Teulade, R. C. Gaudreault, O. Chavignon and E. Moreau, *Eur. J. Med. Chem.*, 2012, **52**, 137; (*c*) A. R. Katritzky, M. Michalska, R. L. Harlow and S. H. Simonsen, *J. Chem. Soc., Perkin Trans. 1*, 1980, 354.

13 L. Hu, J.-D. Jiang, J. Qu, Y. Li, J. Jin, Z.-R. Li and D. W. Boykin, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3613.

14 (*a*) Y. J. Li, H. M. Huang, H. Q. Dong, J. H. Jia, L. Han, Q. Ye and J. R. Gao, *J. Org. Chem.*, 2013, **78**, 9424; (*b*) H. M. Huang, Y. J. Li, Q. Ye, W. B. Yu, L. Han, J. H. Jia and J. R. Gao, *J. Org. Chem.*, 2014, **79**, 1084; (*c*) T. B. Nguyen, M. Corbin, P. Retailleau, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2015, **17**, 4956; (*d*) D. C. Mohan, C. Ravi, V. Pappula and S. Adimurthy, *J. Org. Chem.*, 2015, **80**, 6846; (*e*) Y. Li, H. Xu, M. Xing, F. Huang, J. Jia and J. Gao, *Org. Lett.*, 2015, **17**, 3690; (*f*) Y. Zhu, C. Li, J. Zhang, M. She, W. Sun, K. Wan, Y. Wang, B. Yin, P. Liu and J. Li, *Org. Lett.*, 2015, **17**, 3872; (*g*) S. U. Dighe, S. Mukhopadhyay, S. Kolle, S. Kanojiya and S. Batra, *Angew. Chem., Int. Ed.*, 2015, **54**, 10926.

15 (*a*) J. Dhineshkumar, M. Lamani, K. Alagiri and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 1092; (*b*) Y. P. Zhu,

M. C. Liu, F. C. Jia, J. J. Yuan, Q. H. Gao, M. Lian and A. X. Wu, *Org. Lett.*, 2012, **14**, 3392.

16 (*a*) S. Samanta, S. Jana, S. Mondal, K. Monir, S. K. Chandra and A. Hajra, *Org. Biomol. Chem.*, 2016, **14**, 5073; (*b*) Y. P. Zhu, F. C. Jia, M. C. Liu and A. X. Wu, *Org. Lett.*, 2012, **14**, 4414; (*c*) X. Wu, Q. Gao, S. Liu and A. X. Wu, *Org. Lett.*, 2014, **16**, 2888; (*d*) A. P. Antonchick, R. Samanta, K. Kulikov and J. Lategahn, *Angew. Chem., Int. Ed.*, 2011, **50**, 8605.

17 (*a*) Q. H. Gao, X. Wu, S. Liu and A.-X. Wu, *Org. Lett.*, 2014, **16**, 1732; (*b*) F. L. Yang and S. K. Tian, *Angew. Chem., Int. Ed.*, 2013, **52**, 4929; (*c*) F. Xiao, H. Chen, H. Xie, S. Chen, L. Yang and G. J. Deng, *Org. Lett.*, 2014, **16**, 50.

18 Y. P. Zhu, Z. Fei, M. C. Liu, F. C. Jia and A. X. Wu, *Org. Lett.*, 2013, **15**, 378.

19 (*a*) A. K. Verma, V. Rustagi, T. Aggarwal and A. P. Singh, *J. Org. Chem.*, 2010, **75**, 7691; (*b*) P. Katrun, C. Mueangkaew, M. Pohmakotr, V. Reutrakul, T. Jaipetch, D. Soorukram and C. Kuhakarn, *J. Org. Chem.*, 2014, **79**, 1778.

20 (*a*) A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem. Commun.*, 2015, **51**, 1555; (*b*) K. Pericherla, P. Kaswan, K. Pandey and A. Kumar, *Synthesis*, 2015, 887; (*c*) A. K. Bagdi and A. Hajra, *Chem. Rec.*, 2016, **16**, 1868; (*d*) S. M. Roopan, S. M. Patil and J. Palaniraja, *Res. Chem. Intermed.*, 2016, **42**, 2749; (*e*) K. R. Reddy, A. S. Reddy, R. Shankar, R. Kant and P. Das, *Asian J. Org. Chem.*, 2015, **4**, 573; (*f*) S. K. Rasheed, D. N. Rao and P. Das, *J. Org. Chem.*, 2015, **80**, 9321; (*g*) S. K. Rasheed, D. N. Rao and P. Das, *Asian J. Org. Chem.*, 2016, **5**, 1213; (*h*) K. R. Reddy, A. P. Gupta and P. Das, *Asian J. Org. Chem.*, 2016, **5**, 900; (*i*) D. Dheer, R. K. Rawal, V. Singh, P. L. Sangwan, P. Das and R. Shankar, *Tetrahedron*, 2017, **73**, 4295; (*j*) S. K. Guchhait, A. L. Chandgude and G. Priyadarshani, *J. Org. Chem.*, 2012, **77**, 4438; (*k*) C. Huo, J. Tang, H. Xie, Y. Wang and J. Dong, *Org. Lett.*, 2016, **18**, 1016; (*l*) S. Mishra and R. Ghosh, *Synthesis*, 2011, 3463; (*m*) M. Adib, A. Mohamadi, E. Sheikhi, S. Ansari and H. R. Bijanzadeh, *Synlett*, 2010, 1606; (*n*) S. Kona, R. S. Ravi, V. N. R. Chava and R. S. Perali, *J. Chem.*, 2013, **2013**, 296792; (*o*) C. Ravi and S. Adimurthy, *Chem. Rec.*, 2017, **17**, 1019.

21 (*a*) J. P. Wan, D. Hu, Y. Liu, L. Li and C. Wen, *Tetrahedron Lett.*, 2016, **57**, 2880; (*b*) P. Kaswan, K. Pericherla, H. K. Saini and A. Kumar, *RSC Adv.*, 2015, **5**, 3670.

22 (*a*) K. Monir, A. K. Bagdi, S. Mishra, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2014, **356**, 1105; (*b*) P. Kaswan, K. Pericherla, R. Kant and A. Kumar, *Tetrahedron*, 2014, **70**, 8539; (*c*) X. Meng, J. Zhang, B. Chen, Z. Jing and P. Zhao, *Catal. Sci. Technol.*, 2016, **6**, 890; (*d*) M. M. Xing, M. Xin, C. Shen, J. R. Gao, J. H. Jia and Y. J. Li, *Tetrahedron*, 2016, **72**, 4201.

23 (*a*) L. Cai, F. T. Chin, V. W. Pike, H. Toyama, J. S. Liow, S. S. Zoghbi, K. Modell, E. Briard, H. U. Shetty, K. Sinclair, S. Donohue, D. Tipre, M. P. Kung, C. Dagostin, D. A. Widdowson, M. Green, W. Gao, M. M. Herman, M. Ichise and R. B. Innis, *J. Med. Chem.*, 2004, **47**, 2208; (*b*) N. Masurie, E. Moreau, C. Lartigue, V. Gaumet, J. M. Chezal, A. Heitz, J. C. Teulade and O. Chavignon, *J. Org. Chem.*, 2008, **73**, 5989; (*c*) C. Hamdouchi, C. Sanchez and J. Ezquerra, *Synthesis*, 1998, 867; (*d*) J. Zeng, Y. J. Tan, M. L. Leow and X. W. Liu, *Org. Lett.*, 2012, **14**, 4386; (*e*) L. Ma, X. Wang, W. Yu and B. Han, *Chem. Commun.*, 2011, **47**, 11333; (*f*) K. Monir, A. K. Bagdi, M. Ghosh and A. Hajra, *Org. Lett.*, 2014, **16**, 4630; (*g*) S. Payra, A. Saha and S. Banerjee, *RSC Adv.*, 2016, **6**, 12402; (*h*) S. Mishra, K. Monir, S. Mitra and A. Hajra, *Org. Lett.*, 2014, **16**, 6084.

24 B. R. Nawghare, S. S. Sakate and P. D. Lokhande, *J. Heterocycl. Chem.*, 2014, **51**, 291.

25 (*a*) A. J. Stasyuk, M. Banasiewicz, M. K. Cyrański and D. T. Gryko, *J. Org. Chem.*, 2012, **77**, 5552; (*b*) S. Kundu and B. Basu, *RSC Adv.*, 2015, **5**, 50178; (*c*) F. J. Wang, H. Xu, M. Xin and Z. Zhang, *Mol. Diversity*, 2016, **20**, 659.

26 D. Kour, R. Khajuria and K. K. Kapoor, *Tetrahedron Lett.*, 2016, **57**, 4464.

27 Z. Yang, W. J. Hao, H. W. Xu, S. L. Wang, B. Jiang, G. Li and S. J. Tu, *J. Org. Chem.*, 2015, **80**, 2781.

