HL
http://heteroletters.org

ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 5: (2), 2015, 177-184

SYNTHESIS AND BIOLOGICAL ACTIVITY STUDIES OF SOME NOVEL SUBSTITUTED IMIDAZO[1,2-a]PYRIDINE

Y. Nivid[1], B. S. Jadhav[2], R. S. Kenny[2], B.P.Nazirkar[2], B. R. Thorat[2], B.S Mulgoankar[3] and R. S. Yamgar[3]*

1. Terna Medical College, Nerul, Navi Mumbai, India
2. P. G. Department of Chemistry, Govt. of Maharashtra's Ismail Yusuf College of Arts, Science and Commerce, Jogeshwari (East), Mumbai, India.
3. Patkar-Varde College, Goregaon (West), Mumbai 400062, India.
**E-mail: rsy_chem@rediffmail.com*

ABSTRACT: Reaction of salicylaldehyde and 4-substituted benzoylpropionic acid **1(a-c)** in presence of sodium acetate and acetic anhydride to give 4-substituted 3-(2-(4-phenyl)-2-oxoethyl)-2H-chromen-2-one **2(a-c)** which further treated with bromine in acetic acid to give 4-substituted 3-(1-bromo-2-(4-phenyl)-2-oxoethyl)-2H-chromen-2-one **3(a-c)**.compound **3(a-c)** heated with 2- aminopyridine 4(a-e) in chloroform to give imidazo[1,2-a]pyridine **5(a-n).** The substituted imidazo[1,2-a]pyridine are characterized by NMR and mass spectra. These newly synthesized compounds were tested in vitro for their antibacterial activity

Keywords : benzoylpropionic acid, chromen-2-one , imidazo[1,2-a]pyridine

INTRODUCTION:

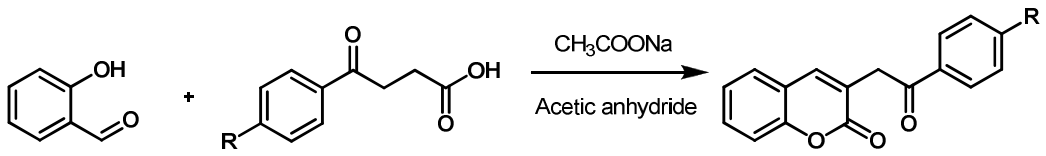
Imidazo[1,2-a]pyridines have been extensively investigated for their applications in the field of pharmacological sciences. They are used in a large area of biological activity such as anticancer,[i] antiviral,[ii] antituberculosis,[iii] antiulcer,[iv] antiinflammatory antifungal,[vi] antibacterial,[vii] antimalerial,[viii] antianxiety,[ix] hypnotics,[x] anticonvulsant,[xi] herbicidal[xii] and Anthelmintics.[xiii] Some of them used for the treatment of congestive heart failure.[xiv] Diaryl substituted imidazo[1,2-a]pyridines have been investigated for its activity as a potential aromatase inhibitors.[xv] Recently, it has been found to be a promising moiety for tunable organic luminescent solids which is a new area of research in physiological studies.[xvi] Imidazo[1,2-a]pyridines are found to exhibit fluorescence properties and has been investigated as biomarkers and photochemical sensors.[xvii]

Very few reports have been found in the literature describing synthesis of Imidazo[1,2-a]pyridine substituted coumarins. Such moieties have been investigated for various activity such as anti-tuberculosis and antimicrobial.[xviii] Biological activities of some 1,3,4-oxadiazolyl substituted imidazo[1,2-a]pyridines have also been investigated.[xix]

RESULTS AND DISCUSSION:

The 4-substituted chromen-2-one [xx] 2(a-c) as shown in scheme I was prepared by condensing salicylaldehyde with 4-substituted benzoylpropionic acid **1(a-c)** in presence of

sodium acetate and acetic anhydride at 90°C after that heated in Conc.HCl, solid separates out.



1(a-c)

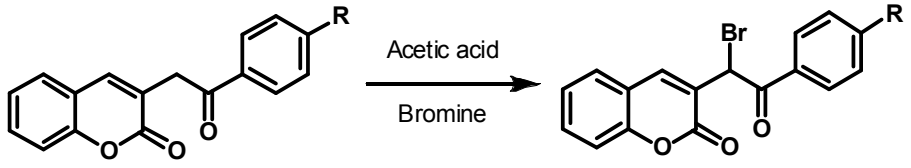
a: R=H
b: R=Br
c: R=OMe

2(a-c)

a: R=H
b: R=Br
c: R=OMe

Scheme I

Bromination of 4-substituted chromen-2-one 2(a-c) was tried using N-bromosuccinimide in chloroform but yield and quality of the product not found satisfactory. However we found that (scheme 1) using bromine in acetic acid gives good yield with simple work up. 4-Substituted 3-(1-bromo-2-(4-phenyl)-2-oxoethyl)-2H-chromen-2-one **3(a-c)** further used without purification.



2(a-c)

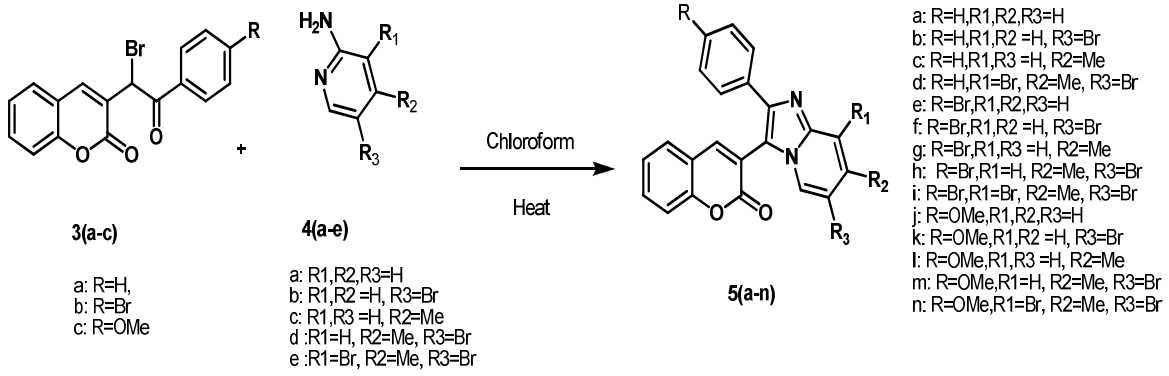
a: R=H
b: R=Br
c: R=OMe

3(a-c)

a: R=H
b: R=Br
c: R=OMe

Scheme II

Substituted imidazo[1,2-a]pyridine have been prepared from 2-amino pyridine with an α-haloketone.[xxi-xxvi]Compound **3(a-c)** was heated with **4 (a-e)** in chloroform to get imidazo[1,2-a]pyridine **5(a-n)** scheme III.



3(a-c)

a: R=H,
b: R=Br
c: R=OMe

4(a-e)

a: R1,R2,R3=H
b: R1,R2 =H, R3=Br
c: R1,R3 =H, R2=Me
d :R1=H, R2=Me, R3=Br
e :R1=Br, R2=Me, R3=Br

5(a-n)

a: R=H,R1,R2,R3=H
b: R=H,R1,R2 =H, R3=Br
c: R=H,R1,R3 =H, R2=Me
d: R=H,R1=Br, R2=Me, R3=Br
e: R=Br,R1,R2,R3=H
f: R=Br,R1,R2 =H, R3=Br
g: R=Br,R1,R3 =H, R2=Me
h: R=Br,R1=H, R2=Me, R3=Br
i: R=Br,R1=Br, R2=Me, R3=Br
j: R=OMe,R1,R2,R3=H
k: R=OMe,R1,R2 =H, R3=Br
l: R=OMe,R1,R3 =H, R2=Me
m: R=OMe,R1=H, R2=Me, R3=Br
n: R=OMe,R1=Br, R2=Me, R3=Br

Scheme III

The newly synthesized compounds were tested in vitro for their antibacterial activity against three microorganisms viz Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa.
The result summarized in table-I
All the synthesized do not show activity seen against Staphylococcus aureus however most of them found active against Escherichia coli and Pseudomonas aeruginosa. Further work in this area is in progress in our laboratory.

Table I

		Mean zone of inhibition (in mm)								
		Escherichia coli ATCC 8739			Staphylococcus aureus ATCC 6538			Pseudomonas aeruginosa ATCC 9027		
Sr.No	Name of the compounds	100 µg/ml	200 µg/ml	300 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml	100 µg/ml	200 µg/ml	300 µg/ml
1	ciprofloxacin	+	+	+	−	−	−	+	+	+
2	5a	−	+	+	−	−	−	−	+	+
3	5b	+	+	+	−	−	−	+	+	+
4	5c	+	+	+	−	−	−	+	+	+
5	5d	+	+	+	−	−	−	+	+	+
6	5e	+	+	+	−	−	−	+	+	+
7	5f	+	+	+	−	−	−	+	+	+
8	5g	+	+	+	−	−	−	−	+	+
9	5h	+	+	+	−	−	−	+	+	+
10	5i	+	+	+	−	−	−	+	+	+
11	5j	+	+	+	−	−	−	−	−	+
12	5k	+	+	+	−	−	−	+	+	+
13	5l	+	+	+	−	−	−	+	+	+
14	5m	+	+	+	−	−	−	+	+	+
15	5n	+	+	+	−	−	−	+	+	+

EXPERIMENTAL:
Melting points of compounds were determined in open capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H NMR spectra were acquired on Bruker (400 MHz), chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Electron impact ionization mass spectra were recorded on Agilent Technologies 5975C MSD detector at 70 eV. Purity of compounds was monitored by TLC on silica F_{254} coated aluminum plates (Merck) as adsorbent and U.V. light and Iodine chamber as a visualizing agent.

General procedure for the synthesis of 4-substituted chromen-2-one. 2(a-c)

A mixture of salicylaldehyde (50 mmol), 4-sustituted benzoylpropionic acid 1(a-c) (50 mmol), sodium acetate (60 mmol) and acetic anhydride (550 mmol) was heated to 90°C till solid dissolved and again precipitated. The mixture was cooled to room temperature and then quenched in 100gm crushed ice. Solid separated out. Conc. HCl (20 ml) added. The yellow reaction mixture was heated to reflux for 3 hrs. The mixture was cooled to room temperature and then filtered and wash with hot ethanol and dried to get solid. yield 45-52% .

3-(2-oxo-2-phenylethyl)-2H-chromen-2-one.(2a) Yield 51% (6.74g) Yellow solid; M.P= 165-166 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.27 (s, 2H), 7.30 -7.28 (dd, *J* = 8.0 Hz, 1H), 7.36-7.34 (d, *J* = 8.0 Hz, 1H), 7.53-7.46 (m,4 H), 7.62-7.58 (m, 1H), 7.70 (s, 1H), 8.07-8.05 (d, *J* = 8.0 Hz, 2H); **MS (ESI) (*m*/*z*):** calcd for $C_{17}H_{12}O_3$, $[M+H]^+$, 265.28; found, 265.1;

3-(2-(4-bromophenyl)-2-oxoethyl)-2H-chromen-2-one.(2b) Yield 48% (8.24g) Yellow solid; M.P= 162-166 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 4.22 (s, 2H), 7.31 -7.27 (t, 1H), 7.36-7.34 (d, *J* = 8.0 Hz, 1H), 7.54-7.46 (m, 2H), 7.65-7.63 (d, *J* = 8.0 Hz, 2H), 7.70 (s, 1H), 7.94-7.92 (d, *J* = 8.0 Hz, 2H); **MS (ESI) (*m*/*z*):** calcd for $C_{17}H_{11}BrO_3$, $[M+2]^+$, 345.17; found, 345;

3-(2-(4-methoxyphenyl)-2-oxoethyl)-2H-chromen-2-one.(2c) Yield 43% (6.33g) Yellow solid; M.P= 135-142 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.89 (s, 3 H), 4.22 (s, 2 H), 6.98-6.96 (d, *J* = 8.0 Hz, 2 H), 7.29-7.25 (m, 1 H), 7.53-7.46 (m, 2 H), 7.70 (s, 1 H), 8.06-8.04 (d, *J* = 8.0 Hz, 2 H); **MS (ESI) (*m*/*z*):** calcd for $C_{18}H_{14}O_4$, $[M+H]^+$, 295.3; found, 295.1;

General procedure for the synthesis of 4-substituted bromo chromen-2-one.3(a-c)

A solution of 4-substituted chromen-2-one 2(a-c) (20 mmol) in 50ml acetic acid was heated to 65°C to get yellow solution. Bromine (22 mmol) was added drop wise at 65°C. After completion of addition, solid precipitated. The reaction was completed as judged by thin layer chromatography. The mixture was cooled to room temperature and then filtered and wash with hot ethanol and dried to get solid. yield 85-90% .

3-(1-bromo-2-oxo-2-phenylethyl)-2H-chromen-2-one.(3a) Yield 85% (5.83g) white solid; M.P= 156-159 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.64 (s, 1H), 7.37 -7.31 (m, 2H), 7.65-7.50 (m, 5H), 8.11-8.08 (m,2 H), 8.24 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{17}H_{11}BrO_3$, $[M+2]^+$, 345.17; found, 345;

3-(1-bromo-2-(4-bromophenyl)-2-oxoethyl)-2H-chromen-2-one.(3b) Yield 86% (7.26g) off white solid; M.P= 172-176 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.54 (s, 1H), 7.37 -7.32 (m, 2H), 7.60-7.56 (m, 2H), 7.66-7.64 (d, *J* = 8.0 Hz, 2H), 7.96-7.94 (d, *J* = 8.0 Hz, 2H), 8.82 (s, 1H) ; **MS (ESI) (*m*/*z*):** calcd for $C_{17}H_{10}Br_2O_3$, $[M+H]^+$, 423.07; found, 422.9;

3-(1-bromo-2-(4-methoxyphenyl)-2-oxoethyl)-2H-chromen-2-one.(3c) Yield 90% (6.72g) white solid; M.P= 152-154 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.89 (s, 3 H), 6.63 (s, 1 H), 6.99-6.97 (d, *J* = 8.0 Hz, 2 H), 7.37-7.30 (m, 2 H), 7.59-7.55 (m, 2 H), 8.09-8.07 (d, *J* = 8.0 Hz, 2 H), 8.24 (s, 1 H **MS (ESI) (*m*/*z*):** calcd for C18H13BrO4, $[M+H]^+$, 374.2; found, 374.2;

General procedure for the synthesis of substituted imidazo[1,2-a]pyridine.5(a-n)

A mixture of substituted 2-aminopyridine 4 (a-e) (1.8 mmol) and 4-substituted bromo chromen-2-one. 3(a-c) (1.5 mmol) in $CHCl_3$ (10 ml) was heated to reflux for 12 hrs. The reaction was completed as judged by thin layer chromatography. The mixture was cooled to room temperature and then filtered to remove insoluble materials. The filtrate was washed with cold saturated aqueous $NaHCO_3$ and then H_2O. The combined organic layer dried over anhydrous Na_2SO_4 and then filtrated. After removing the solvent under reduced pressure, the residue was purified by column chromatography to get solid. yield 35-55% .

3-(2-phenylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5a) Yield 46% (0.23g) yellow solid; M.P= 164-167 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35 – 7.33 (t, 1H), 7.42-7.39 (t, 1H), 7.54-7.45 (m, 5H), 7.76-7.73 (t, 1H), 7.84-7.82 (t, 1H), 7.89-7.88 (d, *J* = 8.0 Hz, 2H),

8.01 (s,1H), 8.09-8.08 (d, *J* = 8.0 Hz, 1H), 8.60-8.59 (d, *J* = 8.0 Hz, 1H); **MS (ESI) (*m*/*z*):**calcd for $C_{22}H_{14}N_2O_2$, $[M+H]^+$, 339.36; found, 339.1;

3-(6-bromo-2-phenylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5b) Yield 42% (0.26g) orange to yellow solid; M.P= 179-181 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.43 – 7.40 (t, 1H), 7.55-7.44 (m, 5H), 7.78-7.75 (t, 1H), 7.87-7.85 (m, 3H), 8.03 (s, 1H), 8.18 (s,1H), 8.51-8.50 (d, 1H) ; **MS (ESI) (*m*/*z*):** calcd for $C_{22}H_{13}BrN_2O_2$, $[M+2]^+$, 419.25; found, 419.0;

3-(7-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5c) Yield 48% (0.25g) yellow solid; M.P= 171-174 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.59 (s, 3H), 7.15 – 7.14 (d, 1H), 7.41-7.38 (t, 1H), 7.53-7.45 (m, 5H), 7.75-7.72 (t, 1H), 7.87-7.86 (d, 2H), 7.94-7.93 (d, 1H), 7.97 (s,1H), 8.36 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{16}N_2O_2$, $[M+H]^+$, 353.39; found, 353.1;

3-(6,8-dibromo-7-methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5d) Yield 36% (0.27g) light brown solid; M.P= 186-188 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.63 (s, 3H), 7.48 – 7.40 (m, 4H), 7.55-7.54 (d, 2H), 7.77-7.74 (t, 1H), 7.87-7.86 (m, 2H), 8.20 (s,1H), 8.47 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{14}Br_2N_2O_2$, $[M+2]^+$, 509.94; found, 510.7;

3-(2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5e) Yield 48% (0.23g) yellow solid; M.P= 158-162 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.89 – 6.85 (t, 1H), 7.37-7.30 (m, 3H), 7.52-7.46 (m, 3H), 7.71-7.61 (m, 4H), 7.80 (s,1H), 7.89-7.87 (d, *J* = 8.0 Hz, 1H) ; **MS (ESI) (*m*/*z*):**calcd for $C_{22}H_{13}BrN_2O_2$, $[M]^+$, 416.02; found, 416.7;

3-(6-bromo-2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5f) Yield 43% (0.25g) yellow solid; M.P= 191-193 ºC ; **^{1}H NMR (400 MHz, DMSO)**: δ 7.42 – 7.40 (t, 1H), 7.58-7.50 (m, 4H), 7.75-7.68 (m, 5H), 8.32 (s,1H), 8.83 (s, 1H) ; **MS (ESI) (*m*/*z*):** calcd for $C_{22}H_{12}Br_2N_2O_2$, $[M+1]^+$, 496.17; found, 497.0;

3-(2-(4-bromophenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5g) Yield 44% (0.22g) brown solid; M.P= 186-187 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.44 (s, 3H), 6.71 – 6.68 (dd, 1H), 7.36-7.32 (t, 1H), 7.48-7.44 (m, 5H), 7.61-7.59 (d, *J* = 8.0 Hz, 2H), 7.66-7.62 (t, 1H), 7.77-7.75 (d, 1H), 7.78 (s,1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{15}BrN_2O_2$, $[M]^+$, 431.28; found, 431.0;

3-(6-bromo-2-(4-bromophenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5h) Yield 42% (0.25g) light green solid; M.P= 194-196 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.58 (s, 3H), 7.42 – 7.40 (t, 1H), 7.54-7.48 (m, 4H), 7.56-7.55 (d, *J* = 8.0 Hz, 2H), 7.71-7.69 (d, *J* = 8.0 Hz, 2H), 7.75-7.72 (t, 1H), 7.99 (s, 1H), 8.15 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{14}Br_2N_2O_2$, $[M+2]^+$, 509.94; found, 510.7;

3-(6,8-dibromo-2-(4-bromophenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5i) Yield 38% (0.26g) light green solid; M.P= 211-214 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.68 (s, 3H), 7.38 – 7.434 (t, 1H), 7.50 – 7.46 (m, 4H), 7.63-7.61 (d, *J* = 8.0 Hz, 2H), 7.69-7.65 (t, 1H), 7.78 (s,1H), 8.02 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{13}Br_3N_2O_2$, , $[M+2]^+$, 589.07; found, 590.9;

3-(2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5j) Yield 85% (5.83g) yellow solid; M.P= 178-182 ºC **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.81 (s, 3H), 6.86 – 6.81 (td, 1H), 6.90-6.88 (d, *J* = 8.0 Hz, 2H), 7.34-7.29 (m, 2H), 7.49-7.43 (m, 2H), 7.70-7.61 (m, 3H), 7.82 (s,1H), 7.88-7.86 (td, *J* = 8.0 Hz, 1H); **MS (ESI) (*m*/*z*):**calcd for $C_{23}H_{16}N_2O_3$, $[M+H]^+$, 369.1; found, 369.1;

3-(6-bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5k) Yield 86% (7.26g) light green solid; M.P= 183-184 ºC **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 3.81 (s, 3H), 6.90-6.88 (d, *J* = 8.0 Hz, 2H), 7.36-7.31 (m, 2H), 7.50-7.44 (m, 2H), 7.59-7.56 (dd, 1H), 7.82 (s,1H), 7.98 (m, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{23}H_{15}BrN_2O_3$, $[M+2]^+$, 449.28; found, 449.0;

3-(2-(4-methoxyphenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5l) Yield 90% (6.72g) light green solid; M.P= 163-166 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.43 (s, 3H), 3.80 (s, 3H), 6.68 – 6.66 (dd, 1H), 6.89-6.87 (d, *J* = 8.0 Hz, 2H), 7.33-7.29 (m, 1H), 7.47-7.41 (m, 3H), 7.63-7.59 (m, 1H), 7.67-7.64 (d, *J* = 8.0 Hz, 2H), 7.76-7.74 (d,1H), 7.79 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{24}H_{18}N_2O_3$, $[M+H]^+$, 383.1; found, 383.1;

3-(6-bromo-2-(4-methoxyphenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5m) Yield 86% (7.26g) light green solid; M.P= 170-174 ºC ; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.48 (s, 3H), 3.80 (s, 3H), 6.89-6.87 (d, *J* = 8.0 Hz, 2H), 7.34-7.31 (m, 1H), 7.53-7.43 (m, 3H), 7.65-7.63 (m, 3H), 7.80 (s,1H), 8.02 (s, 1H);**MS (ESI) (*m*/*z*):** calcd for $C_{24}H_{17}BrN_2O_3$, $[M+2]^+$, 463.31; found, 463.0;

3-(6,8-dibromo-2-(4-methoxyphenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)-2H-chromen-2-one.(5n) Yield 90% (6.72g) yellow solid; M.P= 192-194 ºC **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 2.68 (s, 3H), 3.80 (s, 3 H), 6.89-6.87 (d, *J* = 8.0 Hz, 2H), 7.35-7.31 (td, 1H), 7.49-7.43 (m, 2H), 7.68-7.62 (m, 3H), 7.79 (s,1H), 8.00 (s, 1H); **MS (ESI) (*m*/*z*):** calcd for $C_{24}H_{16}Br_2N_2O_3$, $[M+H]^+$, 541.2; found, 540.9;

REFERENCES:

i. a) Yang Y. J., Yang Y. N., Jiang J. S., Feng Z. M., Liu H. Y., Pan X. D., Zhang P. C., *Chinese Chemical Letters,* 2010, 21(8), 902. b) Buscató E., Wisniewska J. M., Rödl C. B., Brüggerhoff A., Kaiser A., Rörsch F., Kostewicz E., Wurglics M., Schubert-Zsilavecz M., Grösch S., Steinhilber D., Hofmann B., Proschak E. *Future Med Chem.* 2013, 5(8), 865. c) Fu R. G., You Q. D., Yang L., Wu W., Jiang C., Xu X., *Bioorg. Med. Chem., 2010,* 18(22), 8035.

ii. a) Gudmundsson K. S., Williams J. D., Drach J. C., Townsend L. B., *J. Med. Chem.,* 2003, 46(8), 1449. b) Gueiffier A., Lhassani M., Elhakmaoui A., Snoeck R., Andrei G., Chavignon O., Teulade J. C., Kerbal A., Essassi E. M., Debouzy J. C., Witvrouw M., Blache Y., Balzarini J., De Clercq E., Chapat J. P., *J. Med. Chem.,* 1996, 39(14), 2856. c) Chaouni-Benabdallah A., Galtier C., Allouchi H., Kherbeche A., Chavignon O., Teulade J., Witvrouw M., Pannecouque C., Snoeck R., Andrei G., Balzarini J., De Clercq E., Fauvelle ., Enguehard C., Gueiffier A., *Chem. Pharm. Bull.*, 2001, 49, 1631. d) Hamdouchi C., Ezquerra J., Vega Juan A., Vaquero Juan J., Alvarez-Builla J., Heinz Beverly A., *Bioorg. Med. Chem. Lett.,* 1999, 9, 1391. e) Sidwell R. W., Huffman J. H., Call E. W., Warren R. P., Radov L. A., Murray R. J., *Antimicrob. Agents Chemother.,* 1987, 31, 1130. f) Lhassani M., Chavignon O., Chezal J., Teulade J., Chapat J., Snoeck R., Andrei G., Balzarini J., De Clercq E., Gueiffier A., *Eur. J. Med. Chem.,1999,* 34, 271.

iii. a) Moraski G. C., Markley L. D., Cramer J., Hipskind P. A., Boshoff H., Bailey M., Alling T., Ollinger J., Parish T., Miller M. J., *ACS Med. Chem. Lett.*, 2013, 4(7), 675. b) Moraski G. C., Markley L. D., Hipskind P. A., Boshoff H., Cho S., Franzblau S. G., Miller M. J. *ACS Med. Chem. Lett.*, 2011, 2(6), 466. c) Ramachandran S., Panda M., Mukherjee K., Choudhury N. R., Tantry S. J., Kedari C. K., Ramachandran V., Sharma S., Ramya V. K., Guptha S., Sambandamurthy V. K., *Bioorg. Med. Chem. Lett.,* 2013, 23(17), 4996. d) Ramachandran S., Panda M., Mukherjee K., Choudhury N. R., Tantry S. J., Kedari C. K., Ramachandran V., Sharma S., Ramya V. K., Guptha S., Sambandamurthy V. K. *Bioorg. Med. Chem. Lett.,* 2013, 23(17), 4996.

iv. a) Starrett J. E. Jr, Montzka T. A., Crosswell A. R., Cavanagh R. L., *J. Med. Chem.,* 1989 , 32(9), 2204. b) Palmer A. M., Sandra C., Gabriela M., Christof B., Zimmermann P. J., Wilm B., Joerg S., Philipp F. M., Alexander S. W., *Bioorg. Med. Chem.,*2009, 17(1), 368. c) Kaminski J. J., Puchalski C., Solomon D. M., Rizvi R. K., Conn D. J.,

Elliott A. J., Lovey R. G., Guzik H., Chiu P. J. S., Long J. F., Mcphail A. T., *J. Med. Chem.,* 1989, 32, 1686. d) Starrett J. E., Montzka T. A., Crosswell A. R., Cavanagh R., *J. Med. Chem.,* 1989, 32, 2204. e) Kaminski J. J., Hilbert J. M., Pramanik B. N., Solomon D. M., Conn D. J., Rizvi R. K., Elliott A. J., Guzik H., Lovey R. G., Domalski M. S., Wong S., Puchalski C., Gold E. H., Long J. F., Chiu P. J. S., Mcphail A. T., *J. Med. Chem..,* 1987, 30, 2031. f) Kaminski J. J., Perkins D. G., Frantz J. D., Solomon D. M., Elliott A. J., Chiu P. J. S., Long J. F., *J. Med. Chem.,* 1987, 30, 2047.

v. a) Di Chiacchio Anna, Rimoli Maria Grazia, Avallone Lucia, Arena Francesca, Abignente Enrico, Filippelli Walter, Filippelli Amelia, Falcone Giuseppe *Arch. Pharm.,* 1998, 331, 273. b) Abignente E., Arena F., De, Caprariis P., Luraschi E., Marmo E., Lampa E., Vairo G., Somma A., *Farmaco. Ed. Sci.*, 1982, 37, 22.

vi. Lamani R. S., Shetty N. S., Kamble R. R., Khazi A. M., *Eur. J. Med. Chem.,*2009, 44(7), 2828.

vii. a) Mengjun C., Jianding C., Mohamed T., *Inorg. Chem. Commun.*2010, 13(1), 199. b) El-Sayed A. T., *Eur. J. Med. Chem.,*2009, 44(11), 4385. b) Teulade J. C., Grassy G., Girard J. P., Chapat J. P., Simeon D. M., *Eur. J. Med. Chem.,* 1978, 13, 271.

viii. Ebetino F. H., Mazur A., Lundy M. W., Russell R. G. G., PCT Int. Appl., WO 2010033978 A2.

ix. Lopez M. M., Salgado Z. H., Ramirez S. E., Zamudio S., Picazo O., Campos M. E., Naranjo R. E. B., *Drug Dev. Res.,*2010, 71(6), 371.

x. Jia F., Goldstein P. A., Harrison N. L., *J. Pharmacol. Exp. Ther.,* 2009, 328(3), 1000.

xi. Cesur N., Cesur Z., *Farmaco,* 1994, 49, 679.

xii. Ohta K., Minami K., Yoshikawa H., Ishida Y., *Biosci., Biotechnol. and Biochem,* 1993, 57, 1844.

xiii. a) Bochis R. J., Olen L. E., Waksmunski F. S., Mrozik H., Eskola P., Kulsa P., Wilks G., Taylor J. E., Egerton J. R., Ostlind D. A., Olson G., *J. Med. Chem.,* 1981, 24, 1518. b) Bochis R. J., Olen L. E., Fisher M. H., Reamer R. A., Wilks G., Taylor J. E., Olson G., *J. Med. Chem.,* 1981, 24, 1483. c) Bochis R. J., Dybas R. A., Eskola P., Kulsa P., Linn B. O., Lusi A., Meitzner E. P., Milkowski J., Mrozik H., Olen L. E., Peterson L. H., Tolman R. L., Wagner A. F., Waksmunski F. S., Egerton J. R., Ostlind D. A., *J. Med. Chem.,* 1978, 21, 235.

xiv. Yamanaka M., Miyake K., Suda S., Ohhara H., Ogawa T., *Chem. Pharm. Bull. (Tokyo).*, 1991, 39(6), 1556.

xv. Enguehard C., Renou J., Allouchi H., Leger J., Gueiffier A., *Chem. Pharm. Bull.,* 2000, 48, 935.

xvi. Mutai Toshiki, Tomoda Haruhiko, Ohkawa Tatsuya, Yabe Yuji, Araki Koji *Angew. Chem., Int. Ed. Engl.,* 2008, 47, 9522.

xvii. a) Firmansyah D., Ciuciu A. I., Hugues V., Blanchard-Desce M., Flamigni L., Gryko D. T., *Chem. Asian J.*, 2013, 8(6), 1279. b) Leopoldo M., Lacivita E., Passafiume E., Contino M., Colabufo N. A., Berardi F., Perrone R., *J. Med. Chem.,* 2007, 50(20), 5043. c) Hans-Joachim K., Rainer H., Roland B., *Chemis. Ber.,* 1990, 123, 327. d) Tomoda H., Hirano T., Saito S., Mutai T., Araki K., *Bull. Chem. Soc. Jpn.,* 1999, 72(6), 1327. e) Vel zquez-Olvera S., Salgado-Zamora H., Vel zquez-Ponce M., Campos-Aldrete E., Reyes-Arellano A., P,rez-Gonz lez C., *Chem. Central J.,* 2012, 6, 83.

xviii. a) Kumar P. V., Rao V. R., *Ind. J. Chem.*, 2005, 44B, 2120. a) Mohamed H. M., Abd El-Wahab A. H. F., Ahmed K. A., El-Agrody A. M., Bedair A. H., Eid F. A., Khafagy M. M., *Molecules* 2012, 17, 971. c) Sita REDDY, Lucio Comai, Nouri Neamati WO2014028025 A1 University Of Southern California.

xix. a) Oktus F., Cesur N., Satana D., Uzun M., *Turk. J. Chem.,* 2014, 1. b) Cesur Z., Cesur

N., Birteksöz S., Ötük G., Acta Chim. Slov., 2010, 57, 355. c) Shelke S., Salunkhe N., Sangale S., Bhalerao S., Naik N., Mhaske G., Jadhav R., Karale B., *J. Korean Chem. Soc.,* 2010, 54, 59.

xx. a) Bochkov, A. Yu. et al, *Russian Chemical Bulletin, 58(1), 162-169; 2009*. b) Bochkov, A. Yu. et al, *Russian Journal of Organic Chemistry, 44(4), 595-601; 2008.* c) Awasthi, Alok K. and Tewari , Ram S., *Synthesis, (12), 1061-2; 1986.*

xxi. Enguehard, C., Renou, J.L., Allouchi, H., Leger, J.M. and Guiffier, A. 2000. *Chem. Pharm. Bull*, 48: 935

xxii. DiChiacchio A, Rimoli MG, Avallone L, Arena F, Abignente E, Filippelli W 2-Phenylimidazo[1,2-a]pyridine-3-carboxylic acid Derivatives: Synthesis and antiinflammatory Activity . *Arch. Pharm. Pharm.Med. Chem. 1998; 331: 273.*

xxiii. Emam, H. A.; Abdelhamid, A. O. *Indian J Chem 1997*, *36B*, *880*

xxiv. G Trapani; M Franco; L Ricciardi; A Latrofa; G Genchi; E Sanna; F Tuveri; E Cagetti; G Biggio; G Liso. *J.Med. Chem., 1997, 40, 3109-3118*.

xxv. JJ Kaminsky; AM Doweyko. *J. Med. Chem., 1997, 40, 427-436.*

xxvi. A Gueiffier; M Lhassani; A Elhakmoui; R Snoeck; G Andrei; O Chavignion; JC Teulade; A Kerbal; M Essassi; JC Debouzy; JP Witurowo; Y Blache; J Balzarini; E De Clercq; JP Chapat. *J. Med. Chem., 1996, 39, 2856-2859.*

Received on March 7, 2015.