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ARTICLE

Synthesis and characterization of fused imidazole heterocyclic selenoesters and their application for chemical detoxification of $HgCl_2$

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A new series of selenoester derivatives of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine were synthesized under mild conditions using a simple methodology by the reaction of *in situ* generated sodium selenocarboxylates with 2-(chloromethyl)imidazo[1,2-*a*]pyridine/pyrimidine (**3a-b**) in water and ethanol. Excellent yields of phenyl/4-tolyl selenoesters of imidazo[1,2-*a*]pyridine/pyrimidine (**6a-b** and **6e-f**) were obtained in water, whereas 4-methoxyphenyl/4-chlorophenyl/2-thienyl selenoesters of imidazo[1,2-*a*]pyridine/pyrimidine (**6c-d** and **6g-i**) could only be synthesized in ethanol. Further, a series of reactions of **6e** were carried out as a model compound in order to study the reaction behavior of selenoesters with mercury (II) chloride ($HgCl_2$). The deprotection of compound **6e** by $HgCl_2$ was carried out in the presence of K_2CO_3 under different conditions to obtain bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)selenide (**8**) and bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) diselenide (**9**) along with small amount of less soluble bis((imidazo[1,2-*a*]pyrimidin-2-ylmethyl) selanyl)mercury (**10**). The mercury-selenium complex **10** has a short shelf life and decomposes to give HgSe which was characterized using EDX analysis. The structure of compound **9** was established with X-ray crystallography. The formation of HgSe indicates that the selenoester derivatives may prove useful in the treatment of $HgCl_2$ induced toxicity.

1. Introduction

Organoselenium compounds have gained much significance in the last few decades due to their immense biological applications as antioxidant agents,[1] anti-inflammatory agents,[2] anti-tumor agents[3] and for their ability to induce apoptosis in various cancer cells.[4] Organoselenium compounds are known to act as glutathione peroxidase mimetics[5] and their anti-oxidant activity is attributable to their free hydroxyl radical scavenging ability.[1,6] Besides all these biological applications, organoselenium compounds also act as detoxifying agents by coordinating with certain chalcophilic metal compounds such as mercuric chloride ($HgCl_2$) and methylmercury.[7]

$HgCl_2$ poses serious health threats since it is readily soluble in water resources. $HgCl_2$ and methylmercury are toxic due to their large affinity towards thiols thereby depleting glutathione (GSH) level in the body.[8] Inorganic selenium *i.e.* selenite has been shown to have significant protection against mercury induced toxicity by binding with mercury in an equimolar ratio to form a stable Se-Hg complex in plasma and thus reducing the mercury deposition. Organoselenium derivatives such as selenomethionine protects against mercury induced toxicity by increasing the antioxidant defence in biological systems[9] and by demethylation of methyl mercury.[10] Thione and selone derivatives containing a carbon-sulfur and carbon-selenium double bond also mediate the protolytic cleavage of Hg-C bond of organomercurials.[11] Besides Hg-C bond cleavage, the thione and selone derivatives have been shown to be effective in detoxifying organomercurials through formation of less toxic HgS and HgSe nanoparticles.[12] HgSe is an inorganic species which is insoluble in water and organic solvents. Its formation has been observed in marine mammals and sea birds after detoxification of mercury.[13]

Organoselenium compounds such as diaryl diselenides are also supposed to inhibit mercury poisoning through formation of stable Hg-Se complex by firstly getting converted into the selenols. Selenols are more nucleophilic than thiols and form stable complexes with Hg after leaching mercury complexed with thiols,[14(a)] with subsequent oxidation of thiols *in vivo*.[14] Selenoesters act as protected selenols and are stable as compared to the selenol derivatives, they can be deprotected easily to provide selenols and selenolates.[15] Due to their capability of *in vivo* selenol generation, selenoesters easily bind with certain metals present in metalloproteins in biological systems making them important candidates for the treatment of various ailments such as thromboembolic disorders[16] and HIV.[17] However, the interactions of selenoesters with mercury (II) salts have not been extensively explored.

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Electronic Supplementary Information (ESI) available: CIF file, characterization, structure information of compounds **6a-i**, **8-10** and HgSe in detail. CCDC 1564403 (**9**). For ESI and crystallographic data in CIF and other electronic format see DOI: 10.1039/x0xx00000x

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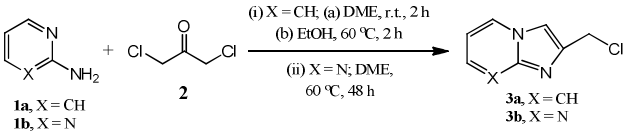
Selenoesters are organoselenium compounds having selenium atom adjacent to carbonyl group. They are precursors of acyl radicals[18] which have been used in the synthesis of α,β-unsaturated ketones[19] and various complex proteins due to accelerated rates of native chemical ligation.[20] Selenoesters have also been explored as liquid crystalline materials.[21] In addition, selenoester derivatives have found to exhibit significant anti-tumor activities[22] and have potential as multi-targeted therapeutics for the treatment of alzheimer's disease.[23] They also act as multidrug resistance reversing agents in cancer cells.[24] These relatively labile organoselenium derivatives can be prepared by the cleavage of diselenides with various metals,[25] polyethylene glycol-400/ hypophosphorous acid,[26] sodium borohydride[27] or rongalite[28] as reductive system followed by addition of acyl chlorides or acid anhydrides as well. PhSeZn-halides[29] and tributyltin aryl selenides[30] also react with acid chlorides under mild conditions to give various aromatic and aliphatic selenoesters. An alternative simple and metal free method involves the reaction of aroyl chlorides with sodium hydrogen selenide followed by addition of alkyl halides using water as the solvent to give selenoesters as products.[31]

The heterocyclic selenoesters based on thiophene moiety have been synthesized and studied extensively for their electrochemical behavior.[32] Selenoester derivatives of heterocycles such as dihydropyrimidinone have been known for their activity against alzheimer's disease.[23] Imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine are two fused heterocyclic systems with a bridgehead nitrogen atom and their derivatives have been known for a long time for their antibacterial, antifungal[33] and anti-inflammatory[34] activities. There are few reports related to the synthesis of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine selenide derivatives.[35] However, the area of imidazo[1,2-*a*]pyridine/pyrimidine selenoesters and metal selenides synthesis has not been explored yet.

Keeping the above discussed points in mind, in the present work, a series of selenoester derivatives (**6a-i**) of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine have been synthesized under mild conditions using water and ethanol as solvents followed by their deprotection in the presence of combined system of K_2CO_3 and $HgCl_2$ under different conditions. The formation of complex **10** and HgSe shows that there is a great possibility that selenoesters may prove useful for the treatment of toxicity caused by $HgCl_2$ in biological systems.



Scheme 1 Synthesis of 2-(chloromethyl)imidazo[1,2-*a*]pyridine and 2-(chloromethyl)imidazo[1,2-*a*]pyrimidine (**3a-b**)

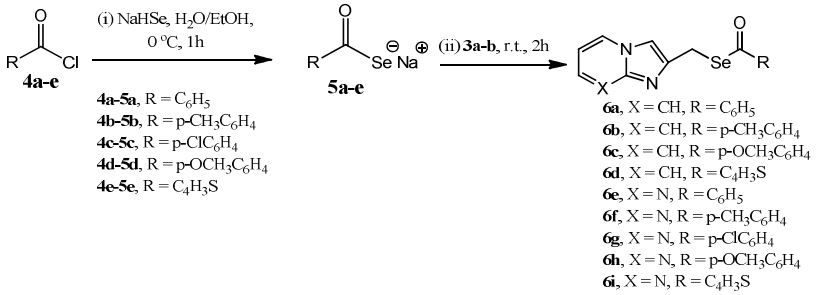
2. Results and discussion

2.1 Chemistry

Imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine selenoester derivatives were synthesized in two steps. The first step in the synthesis of selenoesters involved the preparation of 2-(chloromethyl)imidazo[1,2-*a*]pyridine/pyrimidine (**3a-b**) which were synthesized by the cyclocondensation of 2-aminopyridine[36]/2-aminopyrimidine[37] (**1a-b**) with 1,3-dichloroacetone in the presence of 1,2-dimethoxyethane (1,2-DME) as the solvent in accordance with Tschitschibabin reaction (Scheme 1).

The selenoesters were prepared by adding aroyl chlorides (**4a-e**) to an aqueous solution of sodium hydrogen selenide, generated *in situ* by reduction of elemental selenium with sodium borohydride. The reaction resulted in the *in situ* formation of aryl sodium selenocarboxylates (**5a-e**) to which reactants **3a-b** were added (Scheme 2). After stirring the reaction mixture for few hours, the selenoester (**6a-b** and **6e-f**) were precipitated from the aqueous phase.

Exploring the above methodology, attempt was made to synthesize different selenoesters of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine. However, in case of aroyl chlorides **4c-e** (4-chloro benzoyl, 4-methoxy benzoyl and thiophene-2-carbonyl chlorides respectively), the yield of selenoesters obtained was almost negligible due to the rapid hydrolysis of these aroyl chlorides to the corresponding acids in water. For aroyl chlorides **4c-e**, water was replaced with ethanol for the synthesis of selenoesters (Scheme 2).[23] In ethanol the hydrolysis of aroyl chlorides was repressed and selenoesters (**6c-d**, **6g-i**) were obtained in good yields. The use of ethanol is also favourable by environmental point of view as ethanol is a green solvent.[38]



Scheme 2 General scheme for synthesis of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine selenoesters **6a-i**

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2.2 Mercury detoxification

In recent years, there has been a continuous interest in the synthesis of organic heterocyclic metal chalcogenides, especially organic mercury chalcogenides[39] due to their applications in the synthesis of semiconducting nanoparticles[40] and opto-electronics.[41] Hence, the present work was aimed at studying the selenoester-$HgCl_2$ interactions in order to prepare bis((imidazo[1,2-*a*]pyrimidin-2-ylmethyl)selanyl)mercury (**10**), consequently a series of reactions of selenoesters with $HgCl_2$ were carried out.

The mercury complex **10** may be formed *via* two routes *i.e.* by the deprotection of selenoesters in the presence of potassium carbonate (K_2CO_3) to form corresponding selenolate ion followed by its reaction with $HgCl_2$ or by the reaction of $HgCl_2$ with selenoester catalyzed by K_2CO_3. Herein, initially the deprotection of selenoester **6e** with K_2CO_3 was carried out in THF under an inert atmosphere (Scheme 3). Compound **6e** was hydrolyzed to form potassium imidazo[1,2-*a*]pyrimidin-2-ylmethaneselenolate (**7**) which was subsequently treated with $HgCl_2$ solubilized in THF. The reaction led to the formation of anticipated mercury complex **10**, however, compound **8** was obtained as the major reaction product as evidenced by ^1H, ^{13}C NMR and ESI-MS reported earlier by our group.[35(b)] The mass spectral studies (ES-MS) of the reaction mixture showed the molecular ion peaks corresponding to both of the diselenide **9** and mercury complex **10** at *m/z* 425.1499 and 625.2388, respectively. The selenolate ion (**7**) is formed as the reaction intermediate is proved by the formation of monoselenide **8** and diselenide **9**. The mercury complex **10** eventually decomposed to give HgSe after keeping for 4-5 days in reaction solvent at room temperature. The formation of HgSe as the end product reveals the potential of selenoester derivatives as useful candidates for detoxification of $HgCl_2$.

In the second route, complex **10** was obtained by deprotection of selenoester **6e** by $HgCl_2$ in combination with K_2CO_3 in acetonitrile with the subsequent conversion of **6e** into corresponding acid. It was observed that higher yield of complex **10** was obtained in the latter route. It is important to note that the yield of HgSe obtained depends entirely on the method used for the deprotection of selenoesters rather than the concentration of $HgCl_2$, as ½ equivalent of $HgCl_2$ is sufficient to give 100% yield of mercury complex **10**.[39(a)] The deprotection of thioesters in the presence of Hg^{2+} usually results in the formation of insoluble salts of mercury along with the generation of corresponding thiols due to acid hydrolysis of thioesters in aqueous medium.[42,43] In the present studies, the selenol generated after acid hydrolysis underwent oxidation to form monoselenide **8**.

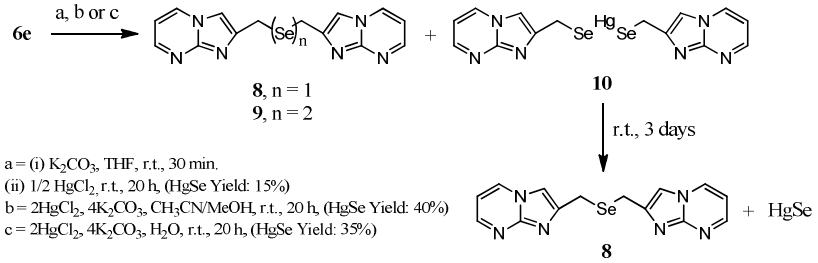
Using the above methodology, the reaction of selenoester **6e** with $HgCl_2$ and K_2CO_3 was also repeated in water. The use of water as the reaction medium for the generation of HgSe as the end product from selenoesters at room temperature indicates the applicability of selenoesters for the detoxification of $HgCl_2$ at physiological conditions.

All the synthesized compounds were characterized with ^1H, ^{13}C NMR and mass spectrometry along with ^{77}Se NMR, HRMS studies and CHNS analysis of some of the representative selenoester derivatives (ESI, page S2-S20†). The ^1H NMR spectra of all the selenoester derivatives (**6a-i**) showed signals of both imidazo[1,2-*a*]pyridine/pyrimidine moiety and the aroyl group present, alongwith a peak around δ 3.5 which indicates the presence of water. The ES-MS of all the selenoester derivatives showed base peak corresponding to $[M+1]^+$. The ^{77}Se NMR spectra of compounds **6a** and **6e** showed peaks at δ 597.05 and δ 597.07 which confirmed the formation of these selenoester derivatives (ESI, page S19†). The formation of the mercury complex **10** was confirmed with mass spectrometry (ESI, page S18†). However, the mercury complex could not be isolated from the reaction mixture due to its less solubility in organic solvents and decomposition to form HgSe. The formation of HgSe was confirmed by EDXRF (Energy dispersive X-ray fluorescence) and the composition of selenium and mercury was found to be 1:1.

2.3 X-ray crystallography

The crystals of bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)diselenide (**9**) were grown by slow evaporation in methanol at room temperature. The diselenide (**9**) crystallizes in $Pca2_1$ space group with two water molecules: a = 21.0903(13); b = 4.5204(3); c = 17.9165(10); α = 90°; β = 90°; γ = 90°; V = 1708.10 Å^3 and Z = 4. The ORTEP and packing diagrams of compound **9** are shown in Fig. 1 and Fig. 2. The details of crystal data and structure refinement have been depicted in Table 1 and the relevant bond lengths and bond angles have been given in Table 2.

The X-ray crystallographic data shows that the Se1-Se2 bond distance is 2.300 Å whereas the Se1-C1 and Se2-C8 bond lengths are 1.964 and 1.968 Å, respectively. From crystal structure parameters it is clear that in compound **9** both the rings are almost perpendicular to each other with Se2-Se1-C1 bond angle 99.98° and Se1-Se2-C8 bond angle 100.58°. Both the imidazo[1,2-*a*]pyrimidine rings are planar with N1-C7-N3-C4 and N5-C14-N6-C10 torsional angles almost planar (179.48° and 179.72°). The distance of N1….O1 of imidazo[1,2-*a*]pyrimidine moiety and water molecule is 2.848 Å while the



Scheme 3 Deprotection of compound **6e** in the presence of K_2CO_3 and $HgCl_2$ under different conditions and formation of HgSe

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Table 1 Crystal data and structure refinement for compound **9**

Parameters	**9**
Empirical formula	$C_{14}\ H_{16}\ N_6\ O_2\ Se_2$
Formula weight	458.25
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P c a 2_1
Unit cell dimensions	a = 21.0903(13) Å, α= 90° b = 4.5204(3) Å, β= 90° c = 17.9165(10) Å, γ = 90°
Volume	1708.10(18) $Å^3$
Z	4
Density (calculated)	1.782 g/cm^3
Absorption coefficient	4.350 mm^{-1}
F(000)	904
Crystal size	0.08 x 0.06 x 0.05 mm^3
Theta range for data collection	1.931 to 25.792°.
Index ranges	-25<=h<=25, -5<=k<=5, -21<=l<=21
Reflections collected	13629
Independent reflections	3030 [R(int) = 0.0303]
Completeness to theta = 25.242°	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3030 / 1 / 224
Goodness-of-fit on F^2	0.988
Final R indices [I>2sigma(I)]	R1 = 0.0319, wR2 = 0.0591
R indices (all data)	R1 = 0.0465, wR2 = 0.0628
Absolute structure parameter	0.492(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.461 and -0.334 $e.Å^{-3}$

N1….O2 distance is 4.832 Å. On the other hand the C12….O2 distance is 2.511 Å. These distances are shorter than the sum of their van der waals radii which indicates that the water molecues play a significant role in the crystallization of the diselenide molecules. Besides the water molecules, the other interactions present are N4…H4, N5…H3 etc.

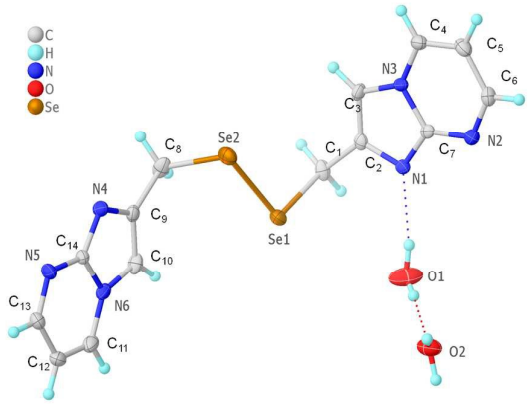

Fig. 1 X-ray crystal structure of bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)diselenide (**9**)

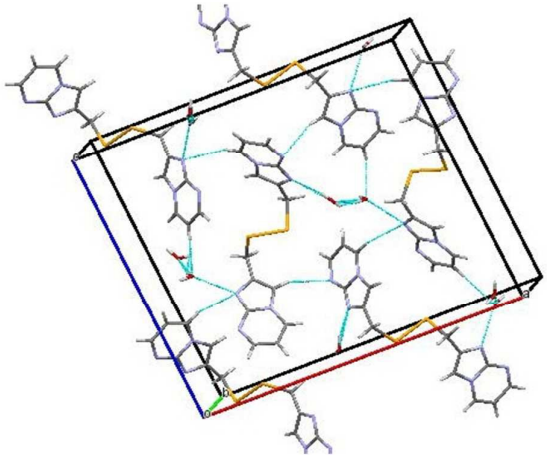

Fig.2 Packing diagram of compound **9**

2.4 Computational Studies

The structures of all the synthesized selenoesters and compounds **8-9** were fully optimized using DFT by GAUSSIAN 03 program at B3LYP level and 6-31 G (d) was adopted as basis set (ESI, Table S1†). The optimized energy was obtained for all the selenoester derivatives and compounds **8-9** and band gap was also calculated (Table S2† and Fig. S1). The results calculated by theoretical studies were in close agreement with those obtained by X-ray crystallography for compound **9** (Table 2). The slight difference in the theoretical and experimental values of Se2-Se1-C1 bond angle may be due to the reason that compound **9** is present in the crystal lattice as a diselenide molecule interacting with two water molecules in solid state while in theoretical calculations the structure has been optimized in gaseous state.

2.5 EDXRF studies

The selenium mercury complex **10** decomposes to give HgSe which

Table 2 Comparison of experimental and theoretical bond lengths, bond angles and dihedral angles for compound **9**

	Experimental value (X-ray)	**Theoretical value (DFT)**
	Bond length (Å)	
Se1-Se2	2.300	2.300
Se1-C1	1.964	1.960
Se2-C8	1.968	1.960
	Bond angle (°)	
C9-C8-Se2	113.37	113.19
Se2-Se1-C1	99.98	109.47
Se1-C1-C2	112.22	112.69
Se1-Se2-C8	100.58	100.44
	Dihedral angle (°)	
C8-Se2-Se1-C1	109.49	109.97
Se2-Se1-C1-C2	72.50	72.77
Se1-Se2-C8-C9	80.38	80.43
N1-C7-N3-C4	179.48	180.00
N5-C14-N6-C10	179.72	-180.00

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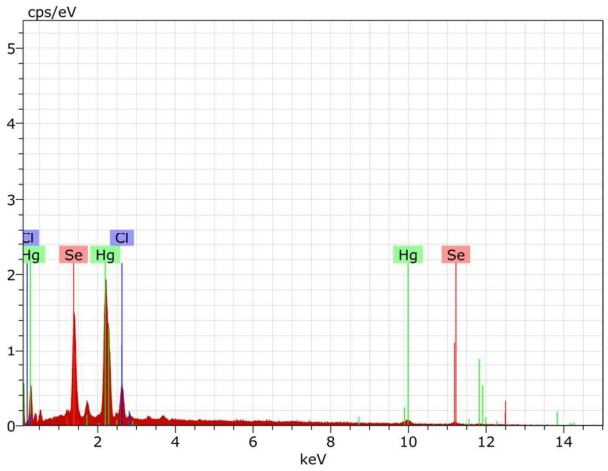

Fig.3 EDX analysis of HgSe formed in acetonitrile

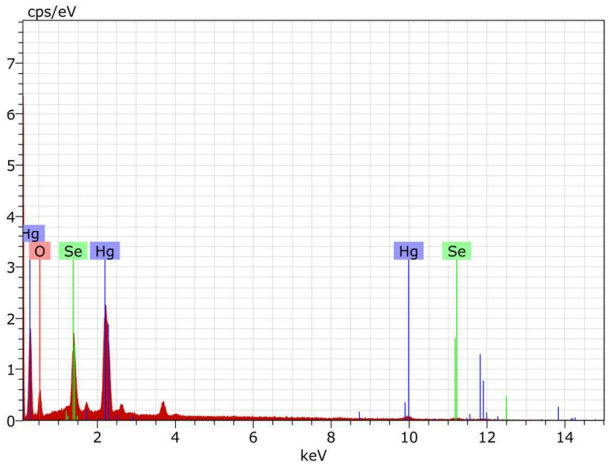

Fig.4 EDX analysis of HgSe formed in water

was characterized using EDX analysis (Fig. 3 and Fig. 4). The EDX spectra showed the presence of well defined peaks corresponding to mercury and selenium. The ratio of Hg and Se in the given samples of HgSe was also determined which comes out to be 1:1 as calculated by EDX analysis.

3. Experimental

3.1 Chemistry

All the reactions involving selenium were carried out in an inert atmosphere of nitrogen. Selenium (CDH, purity >99.0%), 2-aminopyrimidine (Sigma Aldrich), 2-aminopyridine (SRL) and aroyl chlorides (Sigma Aldrich) were purchased and used without any further purification. Products were purified by column chromatography using silica gel (99%, 60-120mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz spectrophotometer in $CDCl_3$ or DMSO-d_6. Infrared spectra were obtained on a Thermo Scientific Fisher spectrometer. Mass spectrometery was carried out on Waters Q-TOF micromass. ^{77}Se NMR was recorded on a Bruker BioSpin GmbH operating at 76.31 MHz. The EDXRF spectra were obtained on a Hitatchi SU8010 scanning electron microscope.

3.1.1 General procedure for the synthesis of selenoesters in water (6a-b and 6e-f)

To a stirred suspension of grey selenium (0.25 g, 3.16 mmol) in deoxygenated water (30 mL) was added sodium borohydride (0.25 g, 6.5 mmol). The reaction mixture was stirred and a colourless solution of NaHSe was formed. Then the reaction mixture was cooled to 0 °C and aroyl chloride was added (3.16 mmol). The reaction mixture was again stirred for 1 h. A yellow solution was formed and 2-(chloromethyl)imidazo[1,2-*a*]pyridine/pyrimidine (0.52 g, 3.15 mmol) was added at 0 °C. A white solid was formed within 2 h. The product was collected by filtration and washed with distilled water (3 x 20 mL). The product was purified with column chromatography using hexane:ethyl acetate (2:3) as the eluent.

3.1.2 *Se*-(imidazo[1,2-*a*]pyridin-2-ylmethyl) benzoselenoate (6a)

Yield: 60%. Brown solid. M. p. 83-85 °C. IR (neat, *v* cm^{-1}): 3131, 3080, 2921, 1707, 1580, 1447, 1312, 1246, 1170, 1013, 887, 769, 707, 624, 457, 429. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (dt, *J* = 6.8, 1.0 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.64 – 7.53 (m, 3H), 7.44 (q, *J* = 7.8 Hz, 2H), 7.16 (ddd, *J* = 9.1, 6.8, 1.2 Hz, 1H), 6.75 (td, *J* = 6.8, 1.0 Hz, 1H), 4.51 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 194.70, 144.81, 143.91, 138.74, 133.73, 132.33, 129.85, 128.81, 128.15, 127.19, 125.52, 125.04, 117.01, 112.60, 110.55, 21.65. ^{77}Se NMR (76.31 MHz, $CDCl_3$): δ (ppm) 597.05. Anal. calcd for $C_{15}H_{12}N_2OSe$ (%): C, 57.14; H, 3.80; N, 8.88. Found: C, 57.16; H, 3.82; N, 8.70. ES-MS: *m/z* 317.90, $[M+H]^+$. HRMS: *m/z* 316.6434, calculated for $[C_{15}H_{12}N_2OSe + H]^+$: 316.0115.

3.1.3 *Se*-(imidazo[1,2-*a*]pyridin-2-ylmethyl) 4-methylbenzoselenoate (6b)

Yield: 65%. White solid. M. p. 90-93 °C. IR (neat, *v* cm^{-1}): 3136, 3036, 1663, 1604, 1497, 1360, 1274, 1167, 1015, 891, 814, 738, 614, 480, 432. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.58 (s, 1H), 7.55 – 7.50 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.12 (ddd, *J* = 9.1, 6.8, 1.3 Hz, 1H), 6.72 (td, *J* = 6.8, 1.1 Hz, 1H), 4.46 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 194.10, 145.09, 144.68, 144.48, 136.29, 129.45, 127.31, 125.47, 124.48, 117.27, 112.24, 110.43, 21.99, 21.72. Anal. calcd for $C_{16}H_{14}N_2OSe$ (%): C, 58.37; H, 4.29; N, 8.51. Found: C, 58.24; H, 4.23; N, 8.48. ES-MS: *m/z* 331.04, $[M+H]^+$.

3.1.4 *Se*-(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) benzoselenoate (6e)

Yield: 55%. White solid. M. p. 79-81 °C. IR (neat, *v* cm^{-1}): 3160, 3088, 1665, 1581, 1447, 1373, 1243, 1198, 1000, 928, 788, 753, 687, 588, 486, 435. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.88 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.48 (dd, *J* = 4.1, 2.0 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.84 (s, 1H), 7.69 (tt, *J* = 7.1, 1.2 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 6.98 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.43 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 193.53, 149.83, 147.38, 144.57, 138.06, 134.67, 134.04, 129.08, 126.70, 109.20, 108.51, 22.03. ^{77}Se NMR (76.31 MHz, CDCl3): δ (ppm)

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597.07. Anal. calcd for $C_{14}H_{11}N_3OSe$ (%): C, 53.18; H, 3.51; N, 13.29. Found: C, 53.11; H, 3.46; N, 13.26. ES-MS: *m/z* 318.00, $[M+H]^+$. HRMS: *m/z* 317.6581, calculated for $[C_{14}H_{11}N_3OSe + H]^+$: 317.0067.

3.1.5 *Se*-(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) 4-methylbenzoselenoate (6f)

Yield: 60%. White solid. M. p. 86-88 °C. IR (neat, *v* cm^{-1}): 3170, 2913, 1912, 1659, 1604, 1500, 1338, 1244, 1163, 985, 890, 785, 697, 621, 456. ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 8.50 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.33 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.57 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.82 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.47 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 194.13, 149.68, 146.91, 144.82, 136.19, 132.87, 129.50, 127.30, 108.78, 108.65, 21.74. Anal. calcd for $C_{15}H_{13}N_3OSe$ (%): C, 54.55; H, 3.97; N, 12.72. Found: C, 54.46; H, 3.85; N, 12.71. ES-MS: *m/z* 332.10, $[M+H]^+$.

3.1.6 General procedure for the synthesis of selenoesters in ethanol (6c-d and 6g-i)

To a stirred suspension of grey selenium (0.375 g, 4.74 mmol) in ethanol (30 mL) was added sodium borohydride (0.36 g, 9.48 mmol). The reaction mixture was stirred and a colourless solution of NaHSe was formed. Then the reaction mixture was cooled to 0 °C and aroyl chloride was added (3.16 mmol). The reaction mixture was again stirred for 1 h. A yellow solution was formed and 2-(chloromethyl)imidazo[1,2-*a*]pyrimidine/pyridine (0.52 g, 3.15 mmol) was added at 0 °C. A white solid was formed within 2 h. The product was collected by filtration and purified with column chromatography using hexane:ethyl acetate (2:3) as the eluent.

3.1.7 *Se*-(imidazo[1,2-*a*]pyridin-2-ylmethyl) 4-methoxybenzoselenoate (6c)

Yield: 49%. White solid. M. p. 101-104 °C. IR (neat, *v* cm^{-1}): 2840, 1682, 1576, 1504, 1416, 1362, 1217, 1101, 1022, 891, 759, 694, 647, 527, 481, 436. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (dt, *J* = 6.8, 1.0 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.58 (s, 1H), 7.16 (ddd, *J* = 9.1, 6.7, 1.2 Hz, 1H), 6.95 – 6.87 (m, 2H), 6.75 (td, *J* = 6.8, 1.1 Hz, 1H), 4.46 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 192.67, 144.71, 144.11, 132.00, 131.61, 129.50, 125.50, 125.10, 116.92, 113.95, 113.51, 112.64, 110.52, 55.54, 21.20. Anal. calcd for $C_{16}H_{14}N_2O_2Se$ (%): C, 55.66; H, 4.09; N, 8.11. Found: C, 55.59; H, 4.00; N, 8.13. ES-MS: *m/z* 347.05, $[M+H]^+$.

3.1.8 *Se*-(imidazo[1,2-*a*]pyridin-2-ylmethyl) thiophene-2-carboselenoate (6d)

Yield: 64%. Pink solid. M. p. 79-81 °C. IR (neat, *v* cm^{-1}): 3133, 3076, 1659, 1494, 1335, 1272, 1188, 1047, 866, 781, 750, 718, 673, 632, 429. ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 8.44 (dt, *J* = 6.8, 1.1 Hz, 1H), 8.00 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.88 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.85 (s, 1H), 7.48-7.41 (m, 1H), 7.25-7.19 (m, 2H), 6.83 (td, *J* = 6.8, 1.1 Hz, 1H), 4.42 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 183.94, 144.11, 142.82, 134.63, 132.68, 132.21, 128.42, 127.81, 126.55, 124.64, 116.05, 111.88, 110.73, 22.03. Anal. calcd for $C_{13}H_{10}N_2OSSe$ (%): C, 48.60; H, 3.14; N, 8.72. Found: C, 48.48; H, 3.09; N, 8.66. ES-MS: *m/z* 323.00, $[M+H]^+$.

3.1.9 *Se*-(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) 4-chlorobenzoselenoate (6g)

Yield: 34%. White solid. M. p. 116-118 °C. IR (neat, *v* cm^{-1}): 3317, 3129, 3076, 1916, 1661, 1572, 1483, 1395, 1295, 1123, 1013, 888, 793, 746, 615, 555, 463, 434. ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 8.83 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.47 (dd, *J* = 4.1, 2.0 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.81 (s, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 6.95 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.45 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 192.34, 157.63, 149.62, 147.42, 144.51, 139.27, 136.57, 134.38, 130.81, 129.02, 128.24, 109.11, 108.39, 22.21. Anal. calcd for $C_{14}H_{10}ClN_3OSe$ (%): C, 47.95; H, 2.87; N, 11.98. Found: C, 47.88; H, 2.79; N, 11.89. ES-MS: *m/z* 351.95, $[M+H]^+$.

3.1.10 *Se*-(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) 4-methoxybenzoselenoate (6h)

Yield: 37%. Grey solid. M. p. 100-102 °C. IR (neat, *v* cm^{-1}): 3002, 2847, 1655, 1573, 1505, 1418, 1342, 1246, 1164, 1019, 887, 783, 646, 613, 456. ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 8.82 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.46 (dd, *J* = 4.1, 2.0 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.79 (s, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.93 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.40 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 191.16, 163.77, 157.62, 149.47, 147.39, 145.09, 134.29, 130.73, 128.99, 113.97, 109.97, 108.98, 108.31, 55.35, 21.62. Anal. calcd for $C_{15}H_{13}N_3O_2Se$ (%): C, 52.03; H, 3.78; N, 12.14. Found: C, 51.95; H, 3.66; N, 12.06. ES-MS: *m/z* 348.04, $[M+H]^+$.

3.1.11 *Se*-(imidazo[1,2-*a*]pyrimidin-2-ylmethyl) thiophene-2-carboselenoate (6i)

Yield: 45%. White solid. M. p. 77-79 °C. IR (neat, *v* cm^{-1}): 3162, 3084, 1659, 1499, 1398, 1242, 1164, 1048, 984, 869, 781, 718, 670, 632, 435. ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 8.86 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.47 (dd, *J* = 4.1, 2.0 Hz, 1H), 8.00-7.95 (m, 1H), 7.86 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.82 (s, 1H), 7.21 (dd, *J* = 4.9, 3.9 Hz, 1H), 6.95 (dd, *J* = 6.7, 4.1 Hz, 1H), 4.44 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 183.69, 149.64, 147.41, 144.64, 142.58, 134.47, 134.32, 132.01, 128.21, 109.15, 108.39, 22.11. Anal. calcd for $C_{12}H_9N_3OSSe$ (%): C, 44.73; H, 2.82; N, 13.04. Found: C, 44.67; H, 2.71; N, 13.15. ES-MS: *m/z* 323.98, $[M+H]^+$.

3.1.12 Synthesis of bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)selenide (8) and bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)diselenide (9)

To a stirred solution of selenoester **6e** (0.0230 g, 0.073 mmol) in 20 mL THF was added K_2CO_3 (0.0100 g, 0.073 mmol) under nitrogen. After all the K_2CO_3 was dissolved, $HgCl_2$ (0.0099 g, 0.0365 mmol) in 10 mL THF was added and the reaction mixture was stirred for 20 h. White precipitate was formed which was collected by filtration and dissolved in methanol. Purification with column chromatography (chloroform) gave compound **8** and **9** as the reaction products.

3.1.13 Bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)selenide (8)

Yield: 65%. White solid.

3.1.14 Bis(imidazo[1,2-*a*]pyrimidin-2-ylmethyl)diselenide (9)

Yield: 11%. White solid. M. p. 165-167 °C. IR (neat, ν cm^{-1}): 3121, 3084, 3002, 2921, 2855, 2766, 1916, 1608, 1500, 1426, 1396, 1245, 1160, 986, 838, 749, 637, 571, 487. ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 8.83 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.47 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.76 (s, 1H), 6.94 (dd, *J* = 6.7, 4.1 Hz,

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1H), 4.20 (s, 2H). ^{13}C NMR (100MHz, DMSO-d_6): δ (ppm) 149.55, 147.51, 144.96, 134.26, 108.92, 108.33, 25.95. Anal. calcd for $C_{15}H_{12}N_2OSe$ (%): C, 36.70; H, 3.52; N, 18.34. Found: C, 36.68; H, 3.43; N, 18.28. ES-MS: *m/z* 425.1499, $[M+H]^+$.

3.1.15 Synthesis of HgSe

A mixture of selenoester **6e** (0.1153 g, 0.365 mmol), $HgCl_2$ (0.1982 g, 0.730 mmol) and K_2CO_3 (0.2017 g, 1.460 mmol) was stirred in 20 mL of CH_3CN and 0.21 mL of methanol or 20 mL of water under inert atmosphere. The reaction mixture was stirred at room temperature for 20 h. Pale yellow solution was formed which was kept at room temperature for 4-5 days. The insoluble black HgSe formed was collected by filtration and washed repeatedly with a mixture of water and acetonitrile and dried under vacuum.

3.1.16 HgSe

The precipitated HgSe obtained by the reaction of selenoester **6e** with $HgCl_2$ and K_2CO_3 in different solvents are detailed below.

In THF Yield: 15%. Black solid.

In CH_3CN Yield: 40%. Black solid.

In water Yield: 35%. Black solid.

3.2 X-ray crystallographic studies

Suitable crystals of compound **9** were obtained by slow evaporation of its solution in methanol. The single-crystal diffraction studies were carried out on a Bruker SMART APEX II CCD diffractometer (Mo-Kα, λ = 0.71073 Å). The crystal structure was solved with the ShelXT-2014/5 structure solution program and by using Olex2 as the graphical interface.[44] The program SAINT (version 8.27B) was used for integration of the intensity of reflections and scaling. The program SADABS was used for absorption correction. The crystal structure was refined using the 2017/1 of ShelXL using Least Squares minimisation.[44] All hydrogen atoms were included in idealized positions, and a riding model was used. Non-hydrogen atoms were refined with anisotropic displacement parameters. The crystal structure was deposited at Cambridge Crystallographic Data Centre and was assigned the number CCDC 1564403.

3.3 Computational studies

The ground state geometries of all the synthesized compounds were optimized using density functional theory (DFT) at the [B3LYP/6-31G(d)] level of theory without any symmetry restriction. All calculations were performed with Gaussian 03 software package.

4. Conclusions

Selenoester derivatives (**6a-i**) of imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine series were prepared using a green methodology by the reaction of precursors **3a-b** with selenocarboxylates (**5a-e**) generated *in situ* through the reduction of elemental selenium with sodium borohydride followed by reaction with aroyl chlorides (**4a-e**) using water or ethanol as solvent. In water as reaction solvent the selenoesters **6a-b** and **6e-f** were obtained in good yields whereas aroyl chlorides (**4c-e**) were hydrolyzed to the corresponding acids. However, the replacement of water with ethanol ceased the hydrolysis of aroyl chorides completely and corresponding selenoesters (**6a-i**) were obtained in good yields. Further, the selenoester derivative **6e** was studied for its reaction behaviour with $HgCl_2$, which is a toxic metal salt and imposes several health problems. The deprotection of compound **6e** with K_2CO_3 in THF was carried out followed by addition of $HgCl_2$, the reaction again gave monoselenide **8** as the major product alongwith compounds **9**, **10** and HgSe in trace amounts. However, the reaction of $HgCl_2$ in the presence of K_2CO_3 with compound **6e** led to deprotection of the selenoester and mercury complex **10** was formed as the major product. A mechanistic study of HgSe formation shows that the mercury complex **10** formed after deprotection of selenoester **6e** undergoes decomposition with elimination of non-toxic mercury selenide (HgSe) to give monoselenide **8**. The structures of all the synthesized compounds were optimized by DFT. The values of theoretically determined parameters were found to be in close agreement with experimental values for compound **9**. The formation of complex **10** and HgSe after the reaction of compound **6e** with $HgCl_2$ shows that in future it may be possible to use selenoester derivatives for the treatment of mercury induced toxicity as these derivatives have high affinity towards $HgCl_2$ and get easily hydrolyzed under physiological conditions.

Conflicts of Interest

There are no conflicts of interest to declare.

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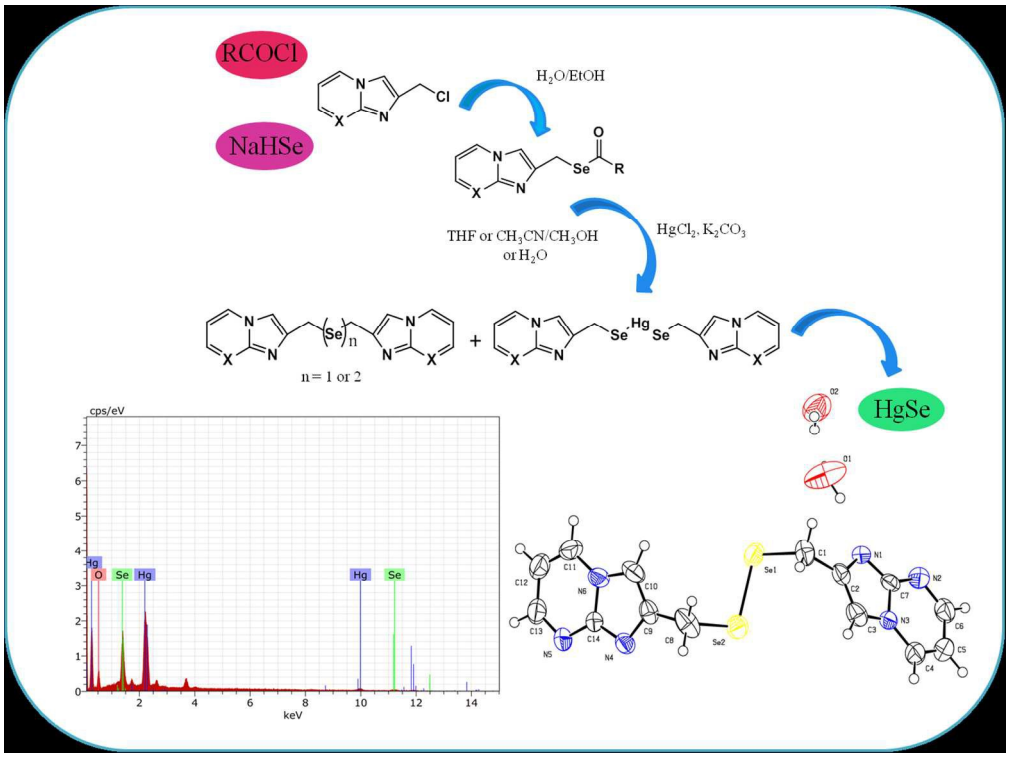

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