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Recent trends in chemistry, structure, and various applications of 1-acyl-3-substituted thioureas: a detailed review

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The interest in acyl thioureas has continually been escalating owing to their extensive applications in diverse fields, such as synthetic precursors of new heterocycles, pharmacological and materials science, and technology. These scaffolds exhibit a wide variety of biological activities such as antitumor, enzyme inhibitory, anti-bacterial, anti-fungal, and anti-malarial activities and find utilization as chemosensors, adhesives, flame retardants, thermal stabilizers, antioxidants, polymers and organocatalysts. In addition, the synthesis, and applications of coordination complexes of these ligands have also been overviewed. The current review is a continuation of our previous efforts in this area, focusing on the recent advancements during the period 2017 to present.

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1. Introduction

The thioureas comprise a broad family of compounds containing the >NC=SN< moiety, the general structure of 1-acyl/aroyl thioureas is shown in Fig. 1.

Thioureas have gained marvelous attention in the last few decades because of their use in the synthesis of several important heterocyclic compounds. Due to the presence of sulfur and nitrogen atoms, which have a multitude of bonding possibilities, their coordination chemistry toward metal ions has become very significant. Their tremendously enhanced ligating properties resulted in the formation of transition metal complex compounds.[1] Their abilities in complex formation and as heterocycle synthons have great significance in organic synthesis. These ligands have a variety of coordination modes and have wide applications in biological systems. Thiourea derivatives also act as organocatalysts and have been used in many reactions.[2,3] Extensive studies showed they play a promising role in the fields of molecular recognition, materials science, agriculture, pharmaceuticals, and biological activities. Various articles have demonstrated the important biological activities of thioureas such as, herbicidal,[4] insecticidal,[5] antimicrobial,[6] antitumor,[7] antiviral,[8] antiparasitic,[9] antidiabetic,[10] fungicidal, pesticidal,[11,12] and urease inhibitory activities.[13,14] The 1*H*-imidazol thiourea derivatives emerged as promising anti-HIV agents.[15] Because of the high relevance of this prestigious family, different aspects deserved researchers' attention and the literature associated with *N*-substituted-*N*-aroyl(acyl) thioureas has been systematically reviewed. The first review on thiourea metal complexes was actualized in 2001 by Koch *et al.*[16] which described the synthesis and coordination chemistry of *N*,*N*-alkyl-*N*′-acyl thioureas.[16] Moreover, topics associated with chemical synthesis have been reviewed by Aly *et al.* in 2007 who focused on aroyl thioureas, their synthesis, and applications.[17] The current review is the furtherance of our previous reviews and updates on these significant and versatile molecules in detail.

Our group published a review in 2014 that included the studies of thiourea metal complexes, their coordination chemistry, and interactions between the molecules,[18] followed by another one in 2017, that discussed the synthetic schemes and reactivity of acyl/aroyl thiourea derivatives, their metal complexes along with biological activities,[19] and further updated in 2019 by the same group, that described versatility of thioureas in heterocyclic syntheses and their multipurpose applications.[20] In addition, some related advances included in

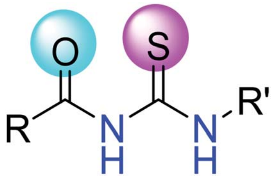

Fig. 1 General structure of 1-acyl/aroyl thioureas.

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2019 review describing novel activities of these compounds.[21] Another review by Lapasam *et al.* in 2020 was related to development of platinum metal complexes containing thiourea ligands and sulfur compound syntheses.[22]

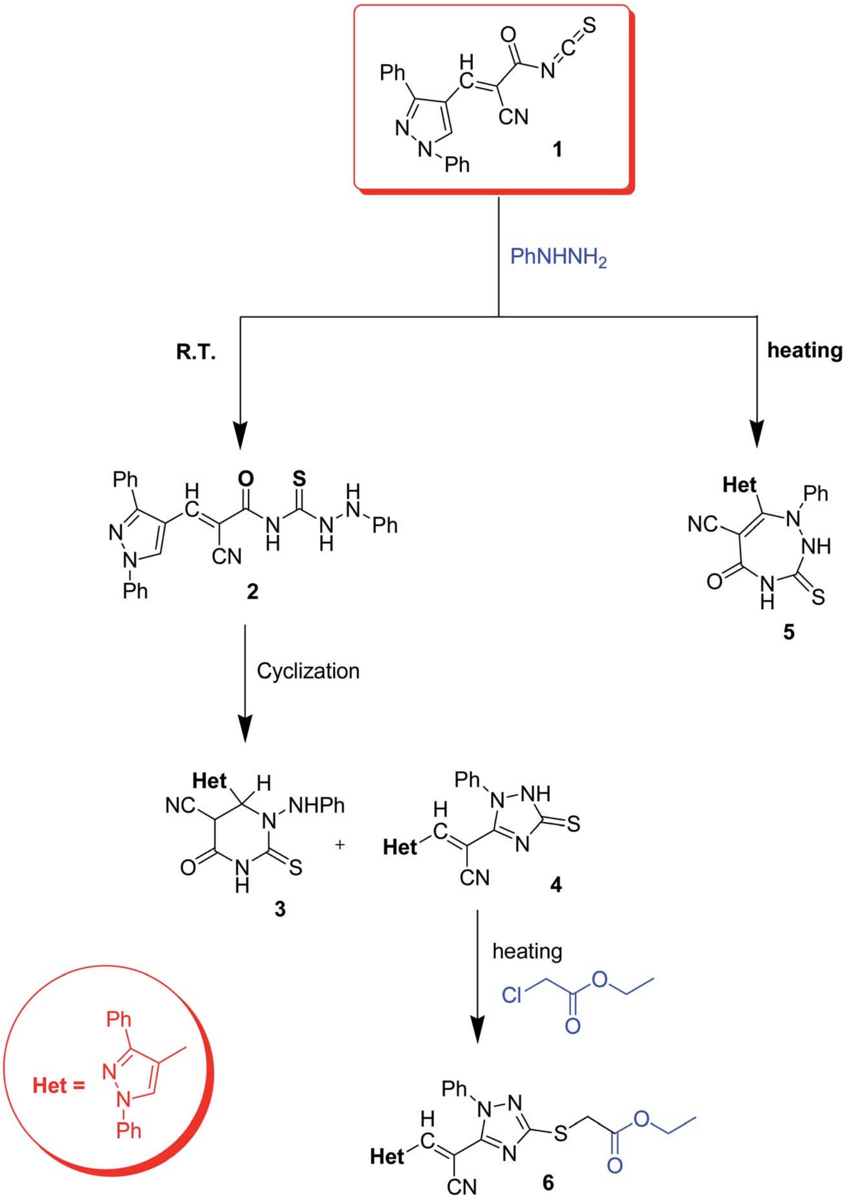
The present review comprises the major advancements that have been taken place in the field of organic synthesis employing thioureas since 2017 when our last review appeared. Medical, synthetic, catalytic and many other fields have been progressed and benefited by these compounds. We have also described various applications of acyl-thioureas along with biological activities in detail which will fascinate the readers.

2. Synthesis

Various novel pathways have been introduced for the synthesis of thiourea derivatives including hybrid-molecule formation[23] and optimization of one-pot syntheses procedures,[24] but the most commonly used procedure is Douglas Dains' method,[25] in which different amines are reacted with *in situ* generated acyl isothiocyanates in dry solvents at specific temperature.[26] Some thioureas have also been synthesized by using ultrasound radiations.[27]

3. Heterocyclization reactions

In this section, recent heterocyclization reactions of thioureas is described. In 2021 Badawy *et al.*[28] synthesized a new series of pyrazole-based heterocycles from 2-cyano-3-pyrazolylpropenoyl isothiocyanate derivative **1** as an intermediate. The Scheme 1 depends on the reaction conditions, thus treatment of 2-cyano-3-pyrazolylpropenoyl isothiocyanate scaffold **1** with



Scheme 1 Synthesis of compounds **2–6** from intermediate **1**.

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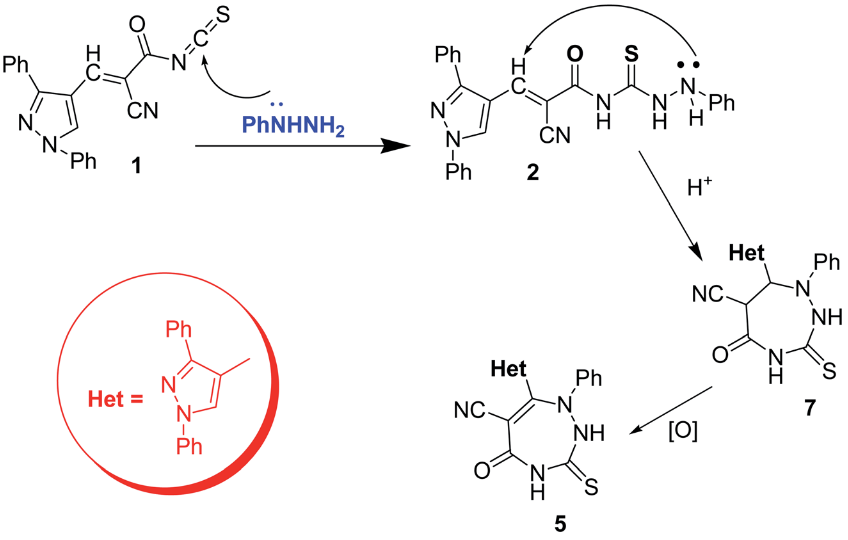

Scheme 2 Plausible mechanism for formation of compound **5**.

phenylhydrazine under room temperature yields a mixture of pyrimidine **3** and triazole compound **4** correspondingly.

The reaction mechanism can be understood *via* the nucleophilic addition of amino group on the intermediate **1** to give compound **2** which undergoes heterocyclization in two different routes to yield 5 (Scheme 2). IR spectra of compound **3** retained the carbonyl group which is absent in **4**. The ^{1}H-NMR of compound **4** indicates one labile hydrogen which confirms the mercaptotriazole form rather thantriazolethione one. Alternatively, the reaction of **1** with phenylhydrazine under heating afforded the compound triazepine **5**, its ^{1}H-NMR shows two labile hydrogens. Lastly, alkylation of **4** with ethyl chloroacetate under heating in ethanol afforded derivative **6**. The prepared compounds were then tested for antioxidant activities, compound **3** exhibits higher activity which may be due to extended conjugation and aromaticity which is absent in other compounds.

Heterocyclic compounds especially five-membered heterocycles displayed many promising pharmacological activities in the medicinal research area. Heterocyclization of thiourea is a good strategy to obtain these prestigious compounds. One such method was used by Kim *et al.*[29] in 2019 on solid state as shown in Scheme 3. Kim developed a solid-phase synthetic method for the synthesis of 2-amino-5-carboxamide thiazoles, this method avoids the formation of undesired isomers. Various amines were introduced in solid-phase synthesis Scheme 4. Merrifield resin **8** was used as a starting compound and reacted with 4-hydroxy-2-methoxybenzaldehyde for 16 h to afford compound **9**. Reductive amination of **9** with amines and $NaBH(OAc)_3$ yields **10**, which is attached with ethoxycarbonyl isothiocyanate **11** in DCM to give thiourea resin **12**. Compound thiourea resin **12** then underwent dehydrative cyclization in the presence of DMF with α-bromoacetophenone **13** to afford compound **14**. Moreover, following the hydrolysis of **16** with NaOH afforded **17**. The resin **17** was cleaved from the polymer support using TFA at room temperature to yield the thiazole **20**. Compound **17** then undergoes amide coupling reaction using EDC HCl, HOBt and amines to afford **18** shown in Scheme 4, resin **18** was cleaved from polymer support under the same conditions used to obtain **20**, the thiazole **19** is obtained. In order to achieve the 4-*tert*-butylthiazole **21**, resin **14** was cleaved at room temperature, all compounds were obtained in good yields.

4. Molecular and crystal structure

There has been much attention given to the conformational and structural properties of 1-(acyl/aroyl)-3-(mono-substituted) thioureas, the conformational flexibility depends upon the substitutions at nitrogen atom on thioureas, these attributes caused these compounds display remarkable activities[30–32] and as fluorescent chemosensors for recognition of many ions.[33] Many articles have been published on the conformational and structural aspects of thioureas.[34]

Saeed *et al.*[35] synthesized and completely characterized the two thiourea derivatives of adamantane-1-carbonyl isothiocyanate **22** using ammonium thiocyanate in very good yields. Their vibrational analysis revealed the intermolecular hydrogen bonds, as confirmed by the analysis of the single crystal molecular structure (Fig. 2). Compound **24 (a)** crystallizes in triclinic system and **24 (b)** has two molecules in the asymmetric unit of the orthorhombic unit cell. They exhibit planar structures due to N–H…O=C H-bonds that generate 6-membered rings. These intermolecular bonding increase the stability of the crystal structures (Scheme 5).

Novel acyl thiourea **26** was prepared and characterized through micro-elemental analysis by González *et al.*[36] Thiourea **26** was prepared by using pivaloyl chloride **25**, KNCS and aqueous ammonia in a 91% excellent yield Scheme 6. The chiral center contains two crystallographically independent molecules

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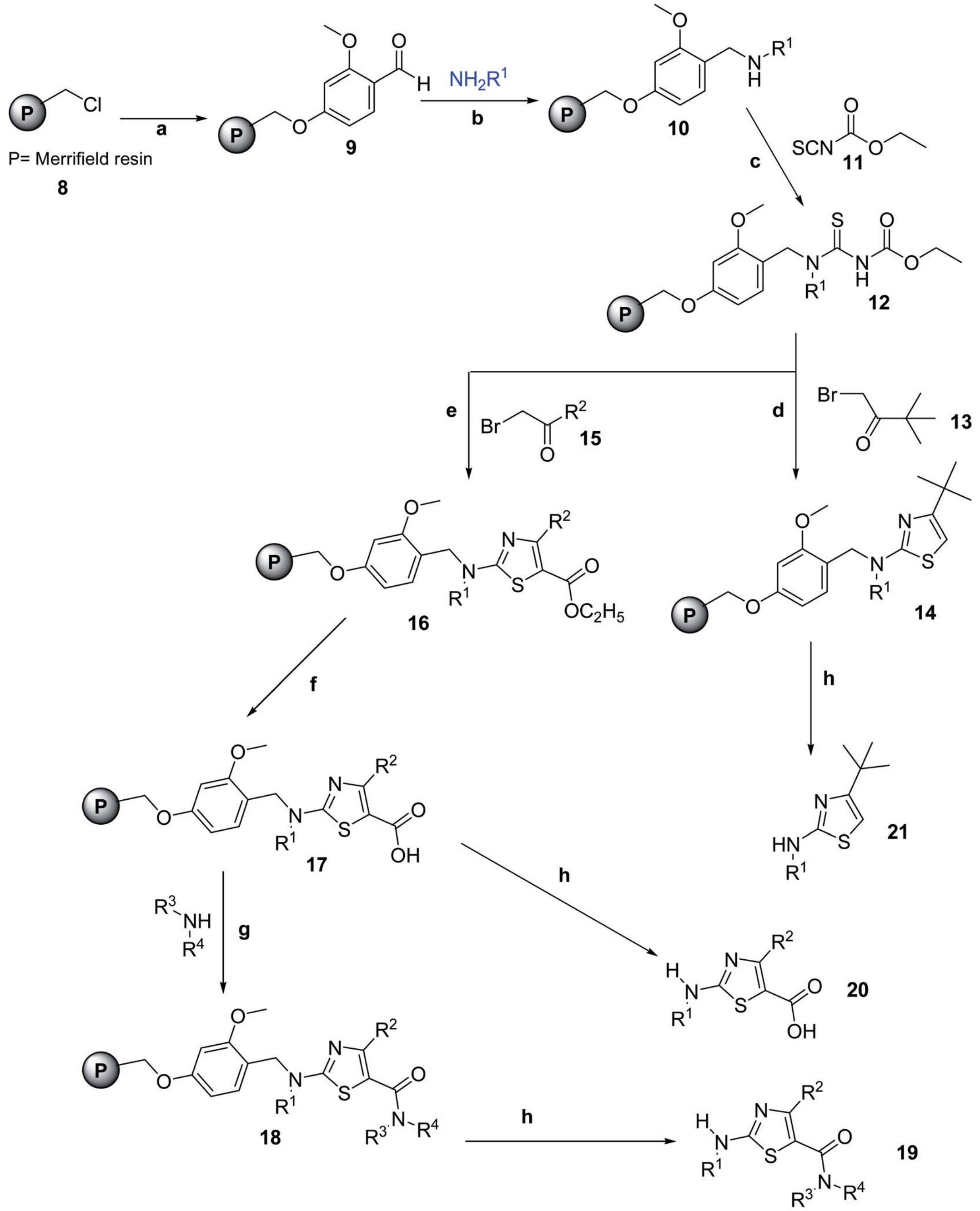

Scheme 3 Preparation of 2-amino-5-carboxamide thiazole derivatives (**19–21**) on solid phase: reagents and conditions (a) 4-hydroxy-2-methoxybenzaldehyde, K_2CO_3, KI, 60 °C, 16 h. (b) $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 1.5 h. (c) DCM, rt, 19 h. (d) DMF, 80 °C, 12 h. (e) TEA, DMF, rt, 2–12 h. (f) 2 M NaOH, DMSO, 60 °C, 72 h (g) EDC HCl, HOBt, DMF, rt, 24 h. (h) TFA/DCM (1 : 2, v/v), rt, 12 h.

A and B with same chemical properties with numbering 1X and 2X (**26**) as shown in Fig. 3. Both molecules display equal bond lengths and angles, and geometric parameters for both showed no unanticipated features. Intermolecular N12–H12B⋯S2 and N22–H22B⋯S1 bonds connect A and B molecules into dimmers, forming pseudo 8 membered ring which are further connected with its neighboring molecules forming infinite chains as depicted in Fig. 4. Single crystal X-ray analysis showed the intermolecular H-bonding between N–H…C═O forming an additionally stabilized six-membered pseudo-ring. Hirshfeld analysis was also performed to confirm these findings.

3,3-Bis(2-hydroxyethyl)-1-(4-methylbenzoyl)thiourea **28** and 3,3-bis(2-hydroxyethyl)-1-(4-nitrobenzoyl)thioureas **27** were prepared by using 4-methylbenzoyl chloride and 4-nitrobenzoyl chloride with ammonium thiocyanate in dry acetone, and the molecular structure of the compounds was evaluated which came out to be like the gas-phase structures Fig. 5 and 6. Hydrogen bonding in the molecular packing led to the

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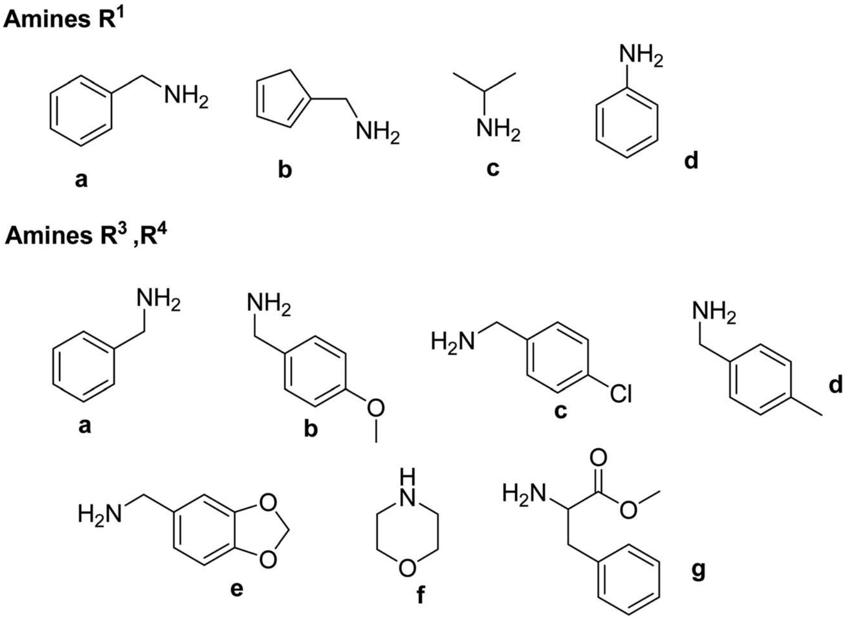
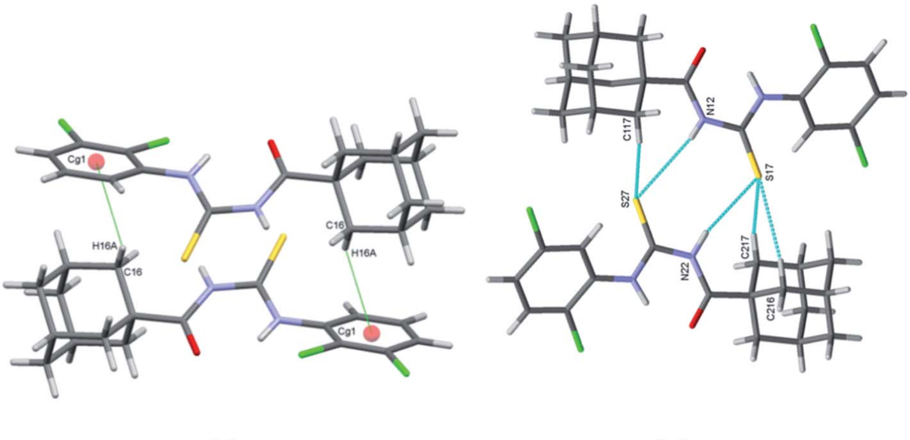


Scheme 4 Building blocks for synthesis of thiazole derivatives (**19–21**).

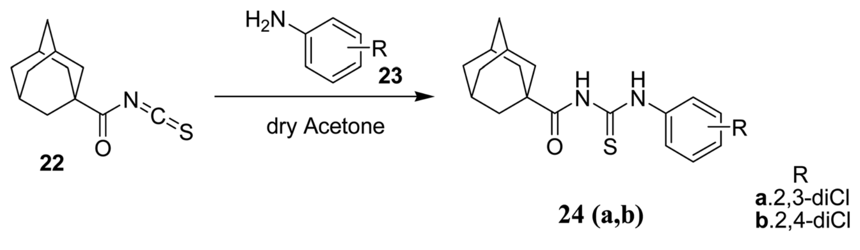


(a) (b)

Fig. 2 Intermolecular interactions present in **24** (a) and (b).

supramolecular layer formations that were further confirmed by the Hirshfeld analysis. These interaction energies provided stability to the molecules. The dihedral and torsional angles of these compounds and spacial arrangements of the substituents were also studied by Tan *et al.*[37,38]

Gumus *et al.*[39] synthesized and characterized a series of four closely related thiourea derivatives **31a–d** and their crystal



Scheme 5 Synthesis of adamantine thioureas **24** (a, b).

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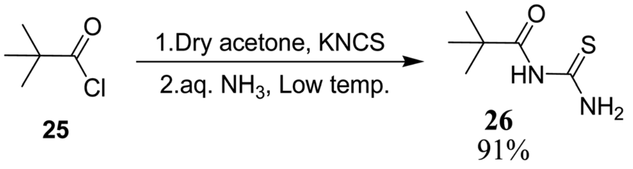

Scheme 6 Synthesis of N-carbamothioylpivalamide **26**.

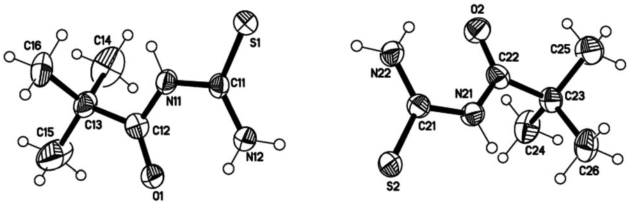

Fig. 3 Molecular structure of compound **26** with anisotropic displacement ellipsoids, molecule **26** with 1X and 2X labeling.

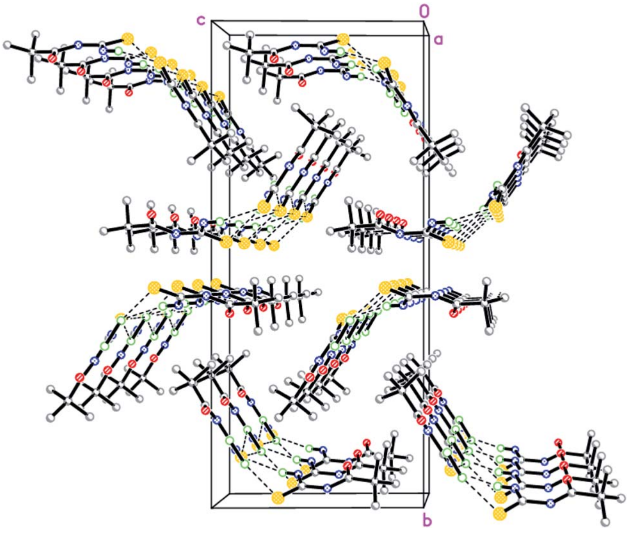

Fig. 4 Crystal packing with intermolecular hydrogen interactions with dotted lines, S, yellow, H, green, N, blue, O, red color.

structures were characterized and studied to evaluate the bonding present in the compounds. 4-Substituted benzoyl chloride **a–d** was reacted with potassium thiocyanate and dibenzylamine **30** in dry acetone to afford the target thioureas **31a–d** in good yields Scheme 7. Intermolecular interactions explained the network in terms of arranged supramolecular units through hydrogen bonding, π–π interactions contributing to the packing of species in the crystals (Fig. 7).

Gumus and coworkers[40] also synthesized novel *N*-(bis(3,5-dimethoxybenzyl)carbamothioyl)-4-*R*-benzamide compounds **33a–d** and these thioureas were characterized by spectroscopic methods and their crystal structures were also determined by single crystal XRD (Fig. 8). These novel derivatives were prepared in the same way as in Scheme 7 by Gumus[39] only the amine is different which is bis(3,5-dimethoxybenzyl)amine **32** Scheme 8. The X-ray crystallography and Hirshfeld surfaces analysis of the novel derivatives **33a–d** exhibits that hydrogen bonding and several weaker interactions *e.g.* N–H⋯S, and weak interactions such as C–H⋯O, C–H⋯S, C–H⋯π and C–H⋯N intermolecular interactions along with π–π stacking cooperative in the stabilization of supramolecular structures.

5. Metal complexes

Thiourea derivatives are used as ligands in metal complexes, their fascinating coordination chemistry along with their derivatives finds a special place in the mind of researchers due to their vast potential applications in various fields. These are found to be excellent ligands because of their structure consisting of lone pair exhibiting sulfur and oxygen atoms that act as ligating centers. Because of the presence of sulphur and nitrogen atoms they act as valuable ligands and coordinate a variety of metal centers and form stable metal complexes.[41] In this section, we will discuss the recent metal complexes of thioureas along with their crystal X-ray diffraction analysis.

Sindhuja *et al.*[42] prepared an Fe(II) catalyst containing acyl thiourea ligands **35** supported on silica nanoparticles, that can be used for the transfer hydrogenation of several carbonyl compounds as shown in Scheme 10. He studied the catalytic activity of **35** towards the transfer hydrogenation of ketones and different carbonyl compounds. The conversions occurred in a moderate to good yields and the catalyst can easily be regenerated from the reaction mixture by centrifugation for further use and can be utilized up to eight cycles without any activity loss. Compound Fe(II)-LSNPs **35** was synthesized by treating ligand **34** with FeCl$_2$ at room temperature for six hours in dry

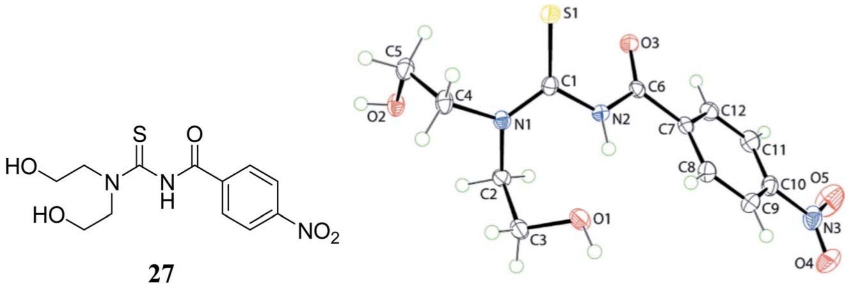

Fig. 5 Molecular structure of **27**.

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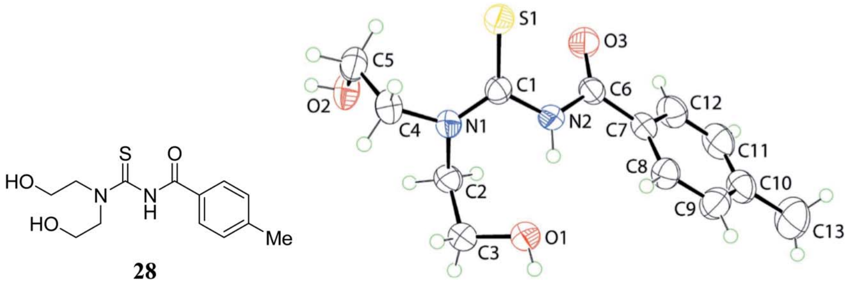
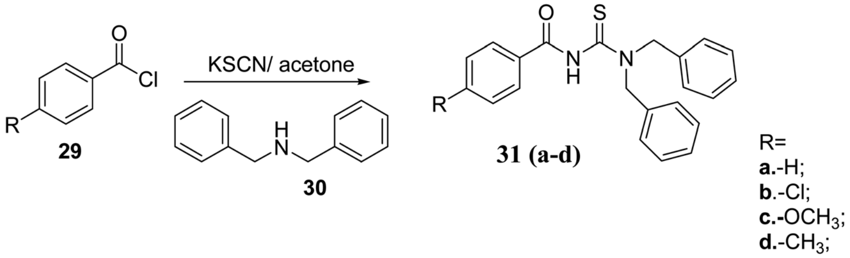


Fig. 6 Molecular structure of **28**.



Scheme 7 Synthesis of **31a–d** compounds.

acetone Scheme 9. In the next step **35** was stirred with carbonyl compound **36** in the presence of KO*t*Bu Scheme 10 for transfer hydrogenation.

A series of Pd(II) complexes **40a–h** with *N*-acyl-*N*,*N*′-(disubstituted) thioureas **38** and phosphine ligands **39** were synthesized by Khan *et al.*[43] using K_2PdCl_4 Scheme 11. These complexes were further characterized by using spectroscopic as well as elemental techniques. FTIR, NMR and single crystal XRD have confirmed the structures of compound **40a** and **40e** (Fig. 9). The square planar geometry has shown the positions of the chelating agents and central atom as well. Various studies of these complexes revealed that they exhibit good antileishmanial activities.

Similar work was conducted by Sathishkumar *et al.*,[44] He synthesized Ru(II)(h6-*p*-cymene) complexes **44a–e** with a new series of pyridine based acylthiourea ligands. These novel complexes were found to be useful as pre-catalysts for the transfer hydrogenation of carbonyl compounds utilizing 2-propanol as a source of hydrogen with KOH base and showing chemoselectivity towards the nitro group in the presence of carbonyl. Acyl chloride **41** was treated with KSCN and 2-(aminomethyl)pyridine **42** in the presence of ethyl acetate to afford acylthiourea ligands **43.** A mixture of $[RuCl_2(h6\text{-}p\text{-cymene})]_2$ and **43** was reacted at room temperature for 5 hours which ultimately afforded the target compounds **44a–e** in good yields Scheme 12. The molecular structure of complex **44a** was confirmed by single crystal XRD analysis Fig. 10, it crystallized in orthorhombic crystal system with inter and intra-molecular hydrogen bonds in the ligands and complex **44a.** The catalysts were also compatible for many heterocycle conversions which include quinine, furfural and other heterocycles.

Ru(II)(η^6-*p*-cymene) complexes **47a–d** having monodentate dibenzosuberenyl substituted aroyl/acyl thiourea ligands have been synthesized and characterized by Rohini *et al.*[45] The complexes **47a–d** were synthesized by the reaction between **45** and **46** in dry toluene Scheme 13. As shown in Fig. 11, the single crystal X-ray analysis showed that the ligand is monodentate and sulfur atom coordinated with Ru(II) resulting in a "3-legged piano-stool" geometry. These catalysts are also used for the transfer hydrogenation (TH) of aldehydes and ketones, as Ru complexes put less steric effects around the [Ru–H] scaffold that initiates the process of TH. These complexes have an exceptional applicability in catalytic transfer hydrogenation. They also have a cytotoxic activity against human cervical, breast, and lung cancer cell lines while maintaining a low toxicity against non-cancerous cells.

Cunha *et al.*[46] synthesized half-sandwich Ru(II) complexes containing acyl thiourea ligands. The reaction of starting material **48** with acyl thioureas **49** in methanol afforded twelve new complexes **50**, **51(a–f)** Scheme 14. They carried out their spectroscopic characterization and cytotoxicity evaluation. Different synthetic routes resulted in differently coordinated complexes. These complexes showed inhibition in the growth of breast and lung cancer cells. Further studies were carried out on the complexes with **(e)** A/B and **(f)** A/B. These complexes inhibit the migration and formation of colony and induced morphology changes.

Gold(I), silver(I) and copper(I) complexes with 2,4,6-trimethylphenyl-3-benzoylthiourea ligand were synthesized by Khan *et al.*[47] The ligand **53** was prepared by reacting aroyl chloride **41c** with **52** Scheme 15, in the next step treatment of **53**

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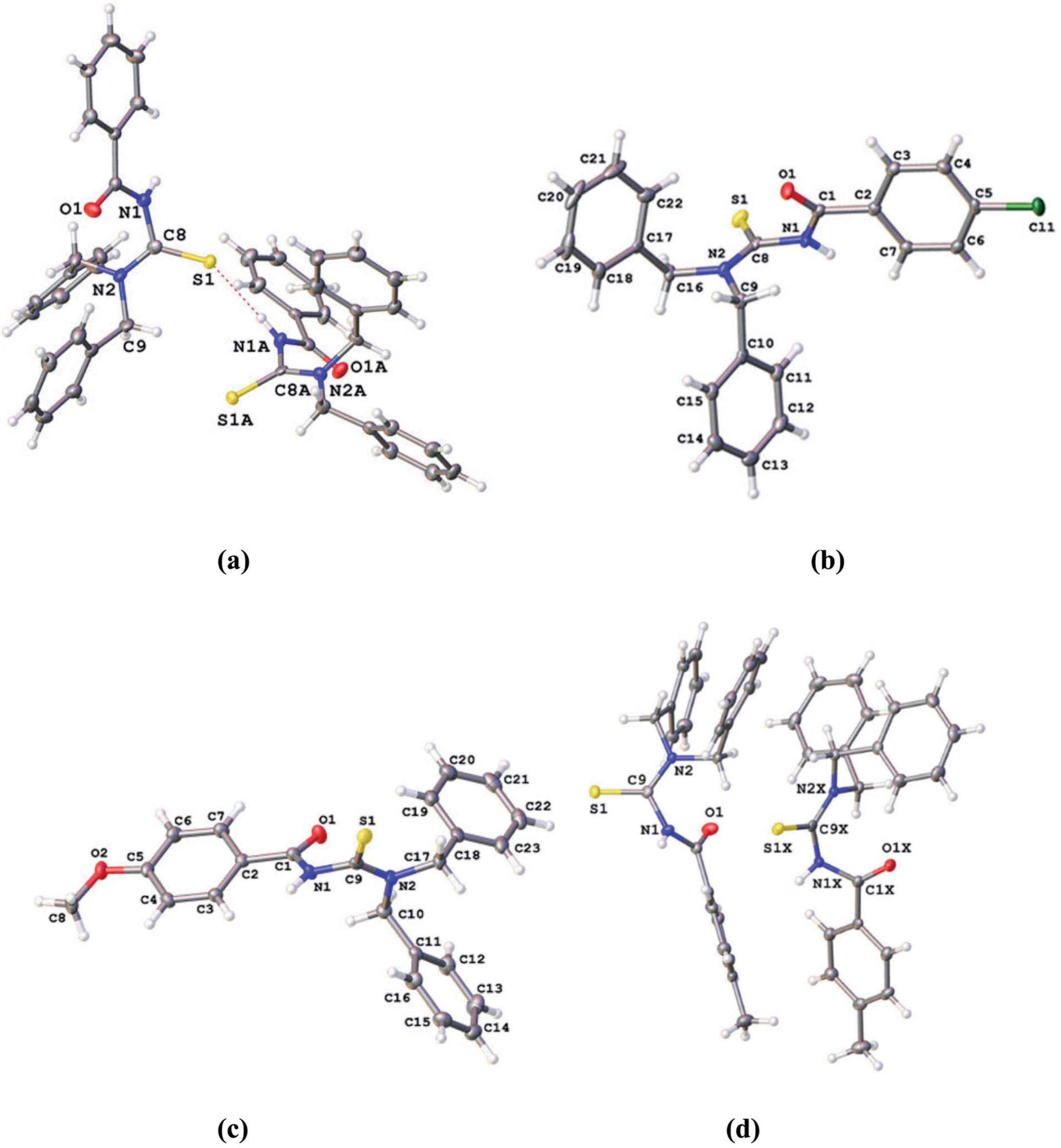
with $HAuCl_4$, $AgNO_3$ and CuI in CH_3CN yields their complexes **54–56.** Their structures were confirmed by X-ray single crystal diffraction, showing the sulfur monodentate coordination mode towards the Au cation (Fig. 12). Complexes with Au/Ag were in the form of fine crystals. The cytotoxicity of these complexes exhibited antibacterial, antifungal, antioxidant, and DNA binding properties.

Plutín *et al.*[48] synthesized seven novel thiourea complexes of Pd(II) and then characterized them by elemental analysis and spectroscopic methods. The ligands **a–g** were combined with Pd(II) by reacting them with **57** in methanol to afford the complexes **58**, **59(a–g)** Scheme 16. Interestingly, mono-substituted thioureas formed N–S coordinated neutral complex, whereas disubstituted one formed the O–S bidentate cationic complex, as shown in Fig. 13. These complexes showed cytotoxicity against tumor cells while the ligands were not cytotoxic. These findings indicated that metal–ligand bindings increase the antitumor activity.

Pérez *et al.*[49] synthesized a novel Pt(II)–metal complex **60** with thiourea ligand **a** bearing morpholine group and characterized it using elemental analysis and spectroscopic methods. Ligand **a** was treated with $[PtCl_2(PPh_3)_2]$ in the presence of methanol



(a) (b)

(c) (d)

Fig. 7 Molecular structures of compounds **31(a–d)**.

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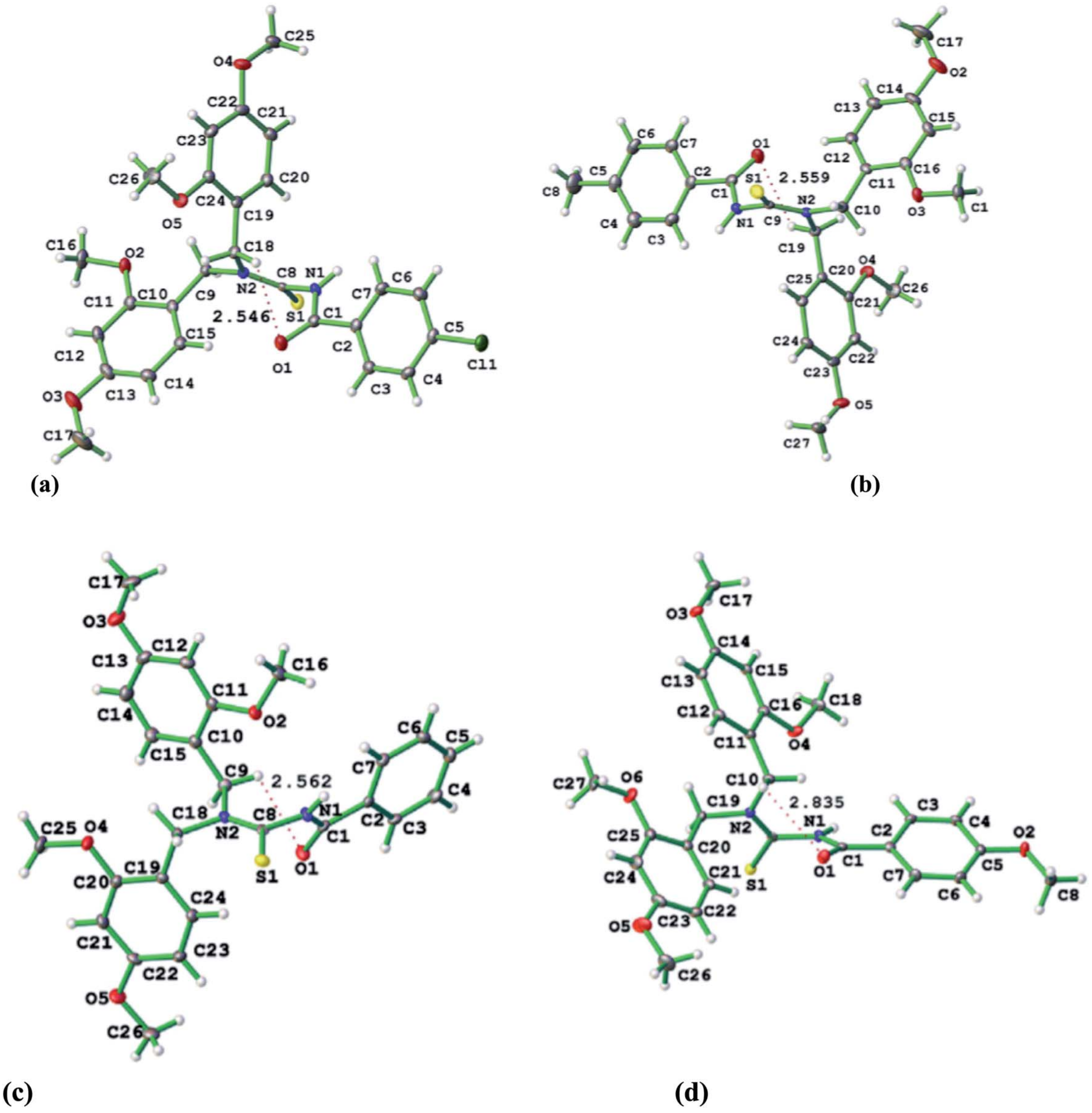
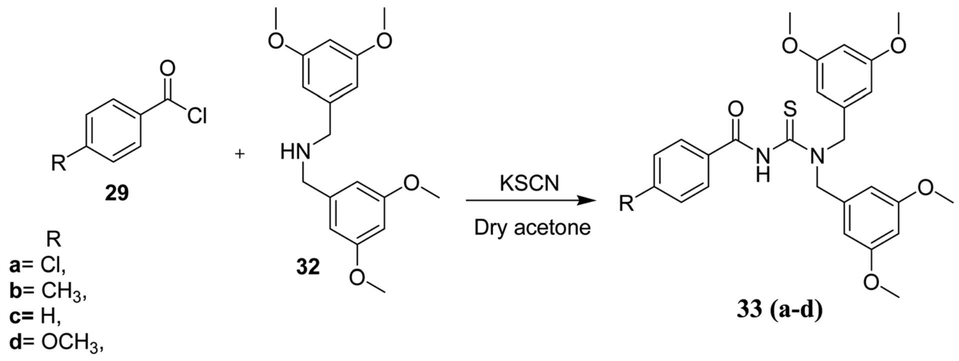


Fig. 8 Crystal structures of the compounds **33(a–d)**.

and KPF_6 which afforded the target complex **60** in 80% yield (Scheme 17). Its single-crystal X-ray structure is shown in Fig. 14, displaying almost great square-planar coordination geometry. Rare C–H···Pt interactions are detected while the crystal is stabilized by weak hydrogen bonds, C–H···F, and C–



Scheme 8 Synthesis of compounds **33a–d**.

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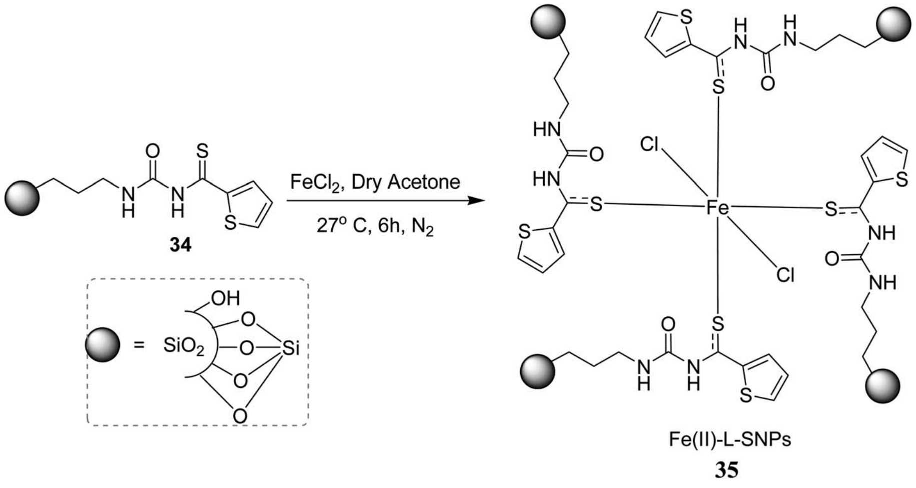
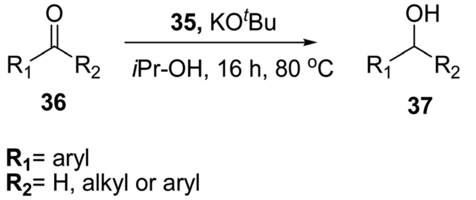


Scheme 9 Synthesis of Fe(II)-L-SNPs **35**.

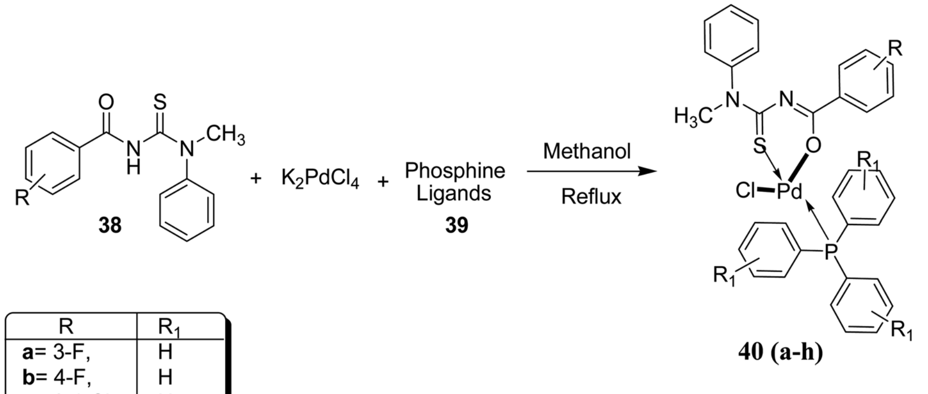


Scheme 10 Transfer hydrogenation of carbonyl compounds **36**.

H···pi stacking interactions. The complex exhibited activity against tumor cells and *Mycobacterium tuberculosis*.

Correa *et al.*[50] synthesized and characterized a ligand *N*-benzoyl-*N*′,*N*′-dibenzyl thiourea and then prepared its Pt(II) complex by reacting it with potassium tetrachloroplatinate(II). He evaluated its interaction with human (HAS) and bovine (BSA) serum albumin. The single crystal X-ray structure provided the spatial arrangements of atoms and geometry (Fig. 15) and Hirshfeld analysis explained the interactions responsible for protein-complex bindings. The X-ray diffraction concludes that Pt atom is coordinated with two chelated thiourea ligands in a square-planar geometry by two sulfur and two oxygen atoms, Fig. 16 shows that molecules in the whole crystal are connected by weak C–H···C and C–H···S along with hydrogen-bonding interactions.

The phenomenon of reversible photo-isomerism using the Pd–thiourea ligand complex **61** was studied and the effect of different solvents on thermal isomerization was explained by Nkabyo *et al.*[51] They also characterized the synthesized *cis*-



R	R$_1$
a= 3-F,	H
b= 4-F,	H
c= 2,4-Cl$_2$,	H
d= 2-CH$_3$,	H
e= 3-F,	*m*-CH$_3$
f= 4-F,	*m*-CH$_3$
g= 2,4-Cl$_2$,	*m*-CH$_3$
h= 2-CH$_3$,	*m*-CH$_3$

Scheme 11 Synthesis of Pd(II) complexes of tri-substituted thiourea.

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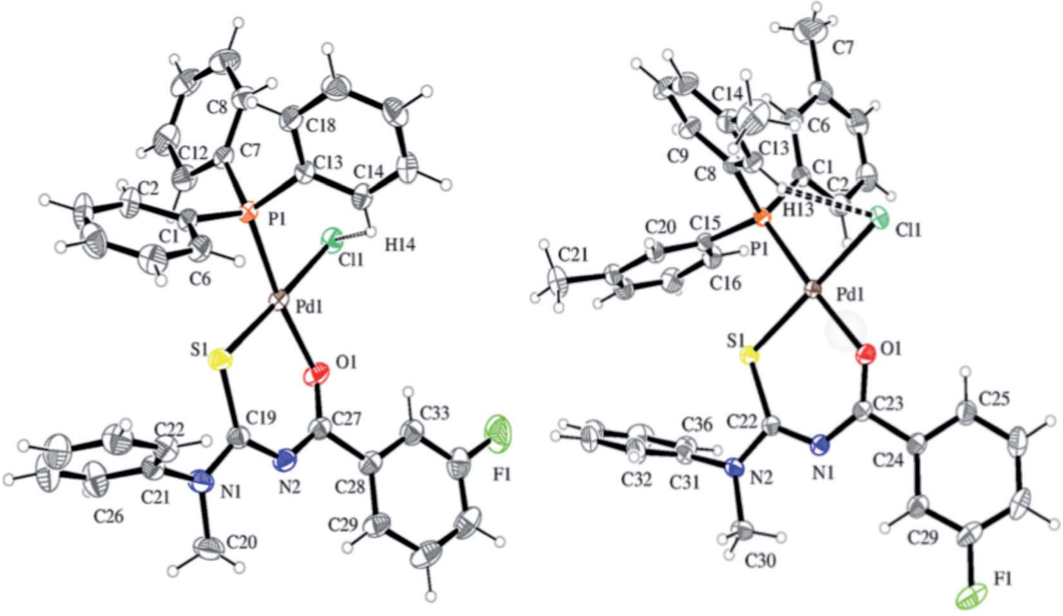
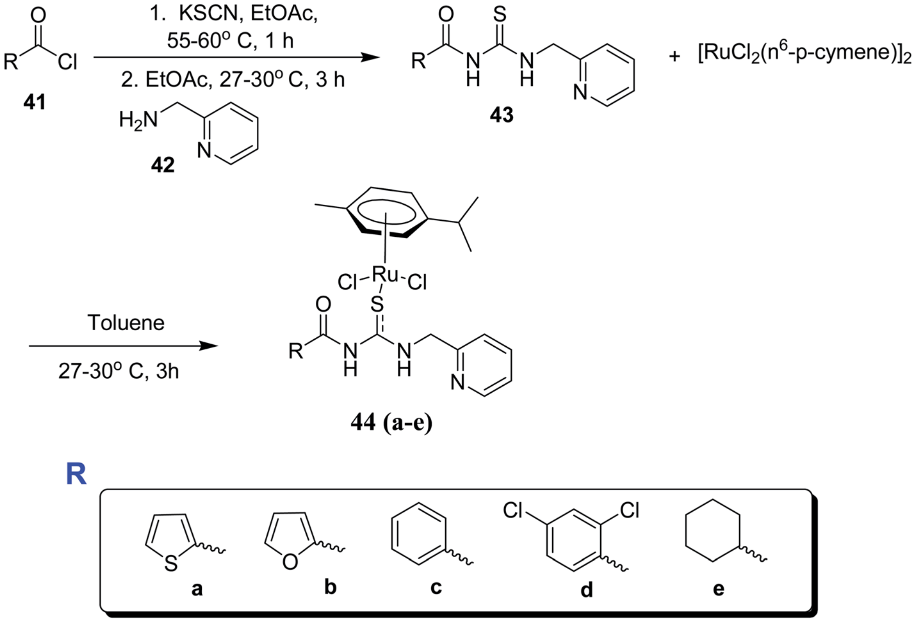


Fig. 9 Molecular structures of **40(a)** and **40(e)** for 30% probability ellipsoids for non-H atoms.

bis(*N*,*N*-diethyl-*N*′-naphthoylthioureato)–palladium(II) complex using NMR and X-ray analysis (Fig. 17).

Nkabyo *et al.*[52] also synthesized and characterized Pd(II) complex cis-bis(*N*,*N*-methyl-ethyl-*N*′-benzoylthioureato)-palladium(II) from an asymmetrically di-substituted ligand *N*,*N*-methylethyl-*N*′-benzoylthiourea. This ligand exists in chloroform as a mixture of **62**, **63** and **64** isomers Scheme 18. The research group also characterized all three isomers using ^{1}H, ^{13}C, HMBC and 1D NOE NMR spectroscopy and single crystal X-ray studies, from these only one crystal of **62** was isolated and studies Fig. 18. These complexes were evaluated based on photo-induced isomerism and its effect on the configurational isomers of the prepared complexes.

In a similar way Nkabyo *et al.*[53] also synthesized Pt(II) complexes Scheme 19 with asymmetrical thiourea ligand *N*,*N*-methylethyl-*N*′-benzoylthiourea in the same manner as described in previous Scheme 18. The Pt(II) complexes exist in three configurational isomers in chloroform namely *cis*-EE-



Scheme 12 Synthesis of Ru(II) complexes with acyl thioureas.

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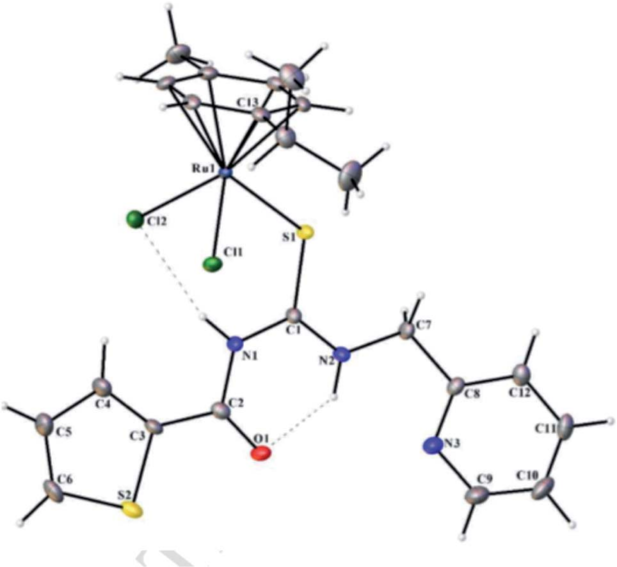
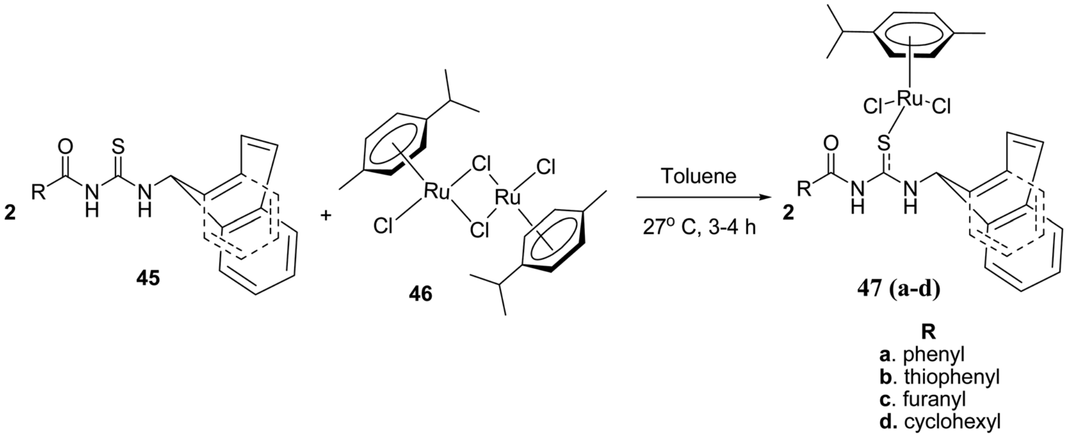


Fig. 10 Molecular structure of **44a**.

$[Pt(L\text{-}\kappa S,O)_2]$, *cis*-ZZ-$[Pt(L\text{-}\kappa S,O)_2]$, and *cis*-ZE-$[Pt(L\text{-}\kappa S,O)_2]$. These complexes were characterized by using ^1H, ^{13}C, HMBC and 1D NOESY NMR spectroscopy and X-ray diffraction (Fig. 19). According to these studies, long-chain and bulky *N*-alkyl substituents showed superior relative distribution of *cis*-ZZ-$[Pt(L\text{-}\kappa S,O)_2]$ isomer than smaller ones and also separated different configurational isomers.

Octahedral diamagnetic complexes **69a–j** of substituted thiourea ligands and cobalt metal were synthesized by Barnard *et al.*[54] The synthesis of complexes **69a–j** involves the reaction between ligand **68** and $CoCl_2 \cdot 6H_2O$ in ethanol at room temperature Scheme 20. These complexes were completely characterized by using ^1H, ^{13}C and ^{59}Co NMR into configurational isomers, and the research group also reported the crystal structures of some of the isolated forms.

Thiourea derivatives **70** and their platinum complexes **71(a, b)** were synthesized (Scheme 21) and characterized by Keskin *et al.*[55] using all the spectroscopic techniques and their structures were also confirmed by single crystal XRD (Fig. 20). The C–H…pi and pi…pi interactions played important roles in the supra-molecular structures of the complexes.



Scheme 13 Synthesis of Ru(II)-*p*-cymene complexes.

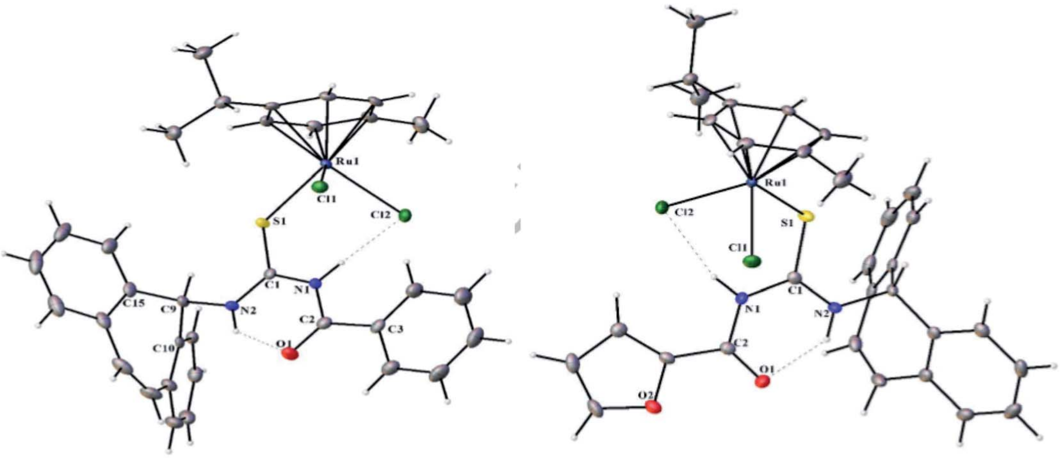


Fig. 11 Molecular structure (50% probability ellipsoids) of **47(a)** and **47(c)** with atomic labeling scheme.

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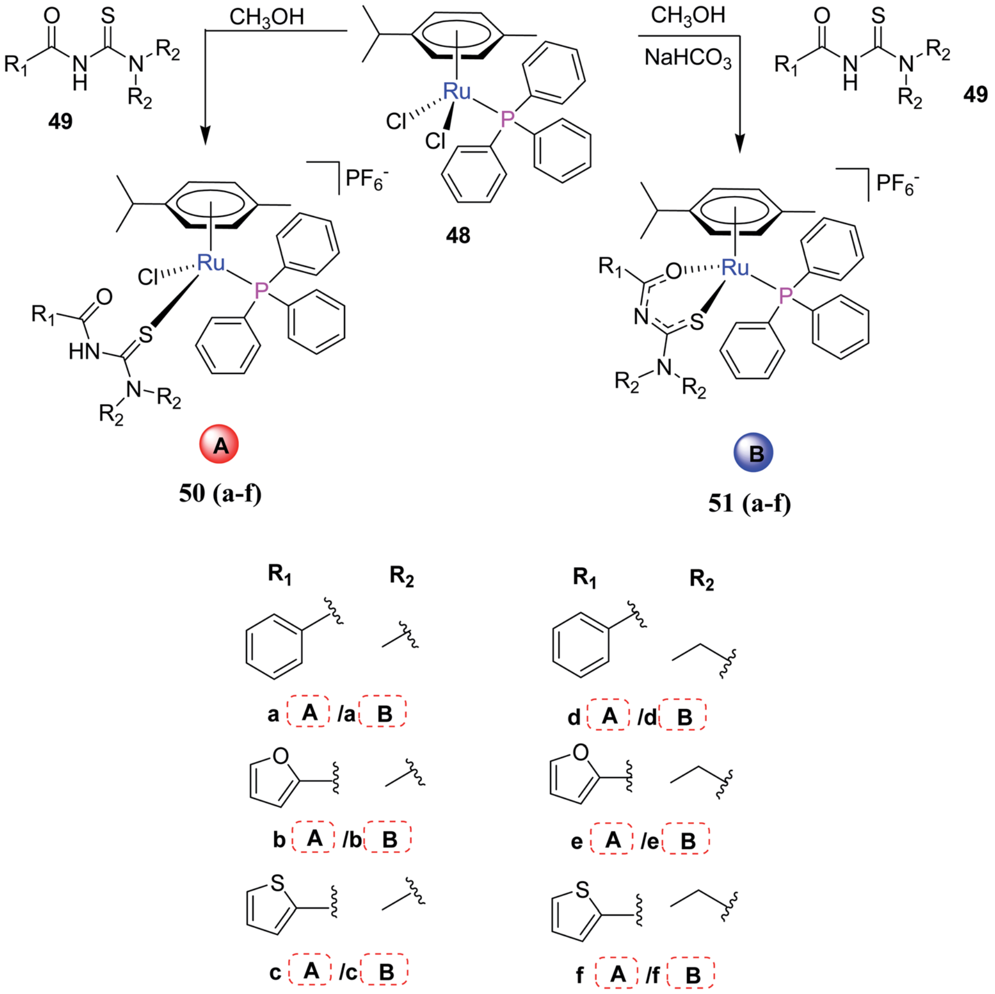
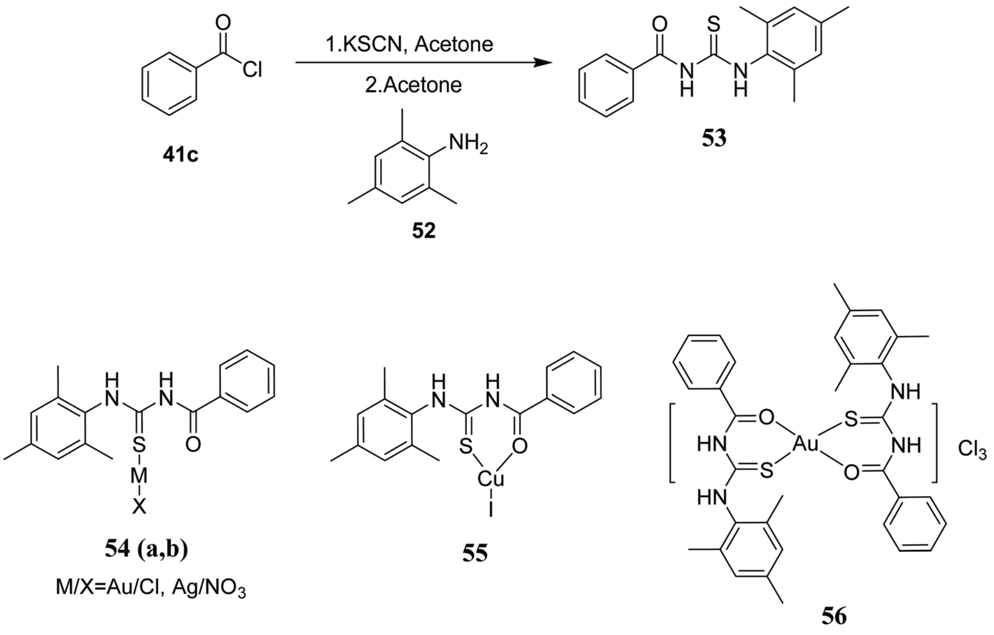


Scheme 14 Synthesis of complexes 50, 51(a–f).



Scheme 15 Synthesis of 53 ligand and its complexes structure 54–56.

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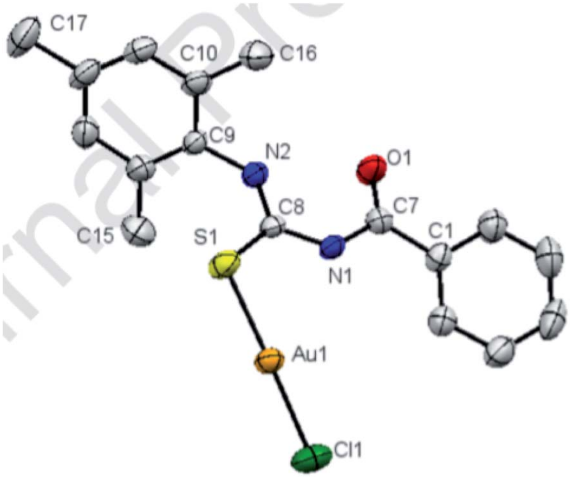


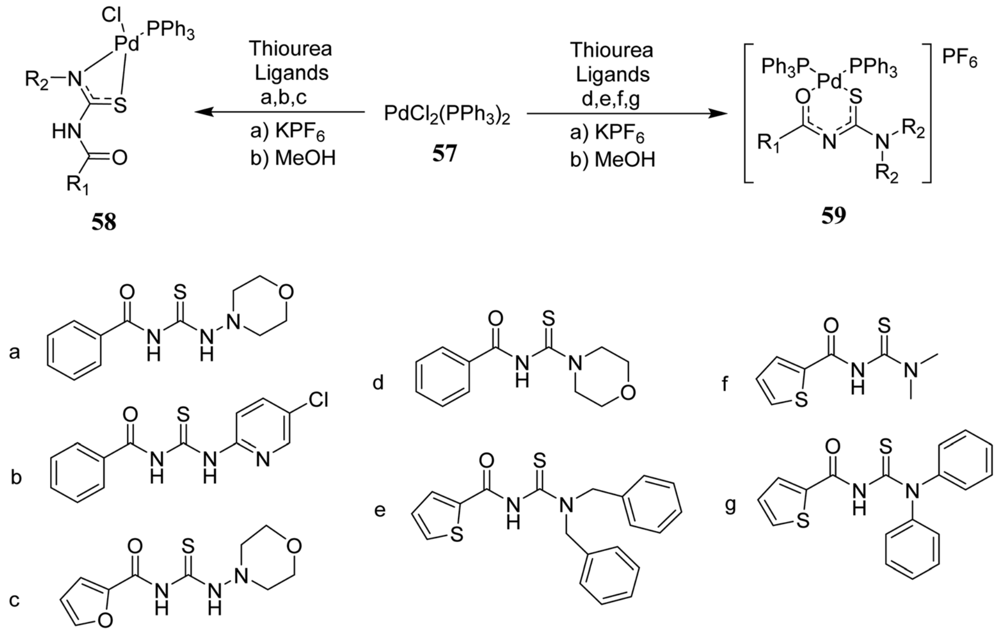
Fig. 12 Molecular structure of complex **54(a)**, with 50% probability ellipsoids.

Binzet *et al.*[56] synthesized four new derivatives of acyl thioureas **72** and their complexes with nickel(II) and copper(II) metals **73a–d** and characterized them using different spectroscopic and elemental analysis techniques. The complexes **73a–d** were prepared by reacting *N*,*N*-dialkyl-*N*,-3-chlorobenzoylthiourea **72** with metal (II) acetate in methanol Scheme 22. The thiourea ligands **72** coordinate with Cu(II), Ni(II) atoms through sulfur and oxygen atoms, two sulfur and two oxygen atoms are mutually *cis* to each other in both complexes. The Hirshfeld analysis and other studies of the prepared compounds have shown the intermolecular contacts and their anti-microbial activities against some strains of bacteria. The molecular structure of the **73d** copper complex is shown in Fig. 21.

Jeyalakshmi *et al.*[57] synthesized new copper complexes **75a–d** by reacting aroyl thiourea ligands **74** and copper(I) bromide in acidic media Scheme 23. The molecular structures and geometry of the complexes **75a**, and **75c** were confirmed by X-ray analysis (Fig. 22). The crystal structure showed tetrahedral geometry of Cu(I) complex, in which the three coordination sites were engaged by sulfur atom from the ligands and the Br occupied the fourth one. The X-ray analysis also confirmed the presence of intramolecular hydrogen bonding between N–H and carbonyl and H.Br bonding between N–H and Br$^-$ ion. The compounds were also examined for their cytotoxic activities against cancer cell lines, compound **75a**, and **75b** exhibited potent activity against HeLa cells.

N,*N*-Disubstituted-4-chlorobenzoyl thiourea ligands **76** were combined with platinum(II) metal to form complexes **77a–d** by Solmaz *et al.*[58] Scheme 24. The complexes were completely characterized by spectroscopic techniques and X-ray analysis. The crystal structure of **77d** (Fig. 23) showed that a square-planar coordination geometry is occurred around the Pt(II) atom by two oxygen and two sulfur atoms from the ligands having *cis* configuration. Their *in vitro* studies had revealed the antibacterial and antifungal activities associated with the complexes **77a–d**.

Sheeba *et al.*[59] prepared novel water-soluble half-sandwich chiral Ru(II)-benzene complexes **81(a, b)** and **82(a–d)** using chiral aroyl thiourea ligands **79**, **80** derived D/L-alanine and $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$**78** in toluene as shown in Scheme 25. These complexes were characterized, and their solid-state structures were confirmed. The X-ray analysis showed monodentate sulfur coordination of thiourea ligands in the complexes, and Ru(II) showed half-sandwich "3-legged piano-stool" geometry Fig. 24. These water-soluble complexes showed enhanced catalytic activity for the enantioselective reduction of ketones.



Scheme 16 Reaction for the synthesis of complexes **58(a–c)** and **59(d–g)**.

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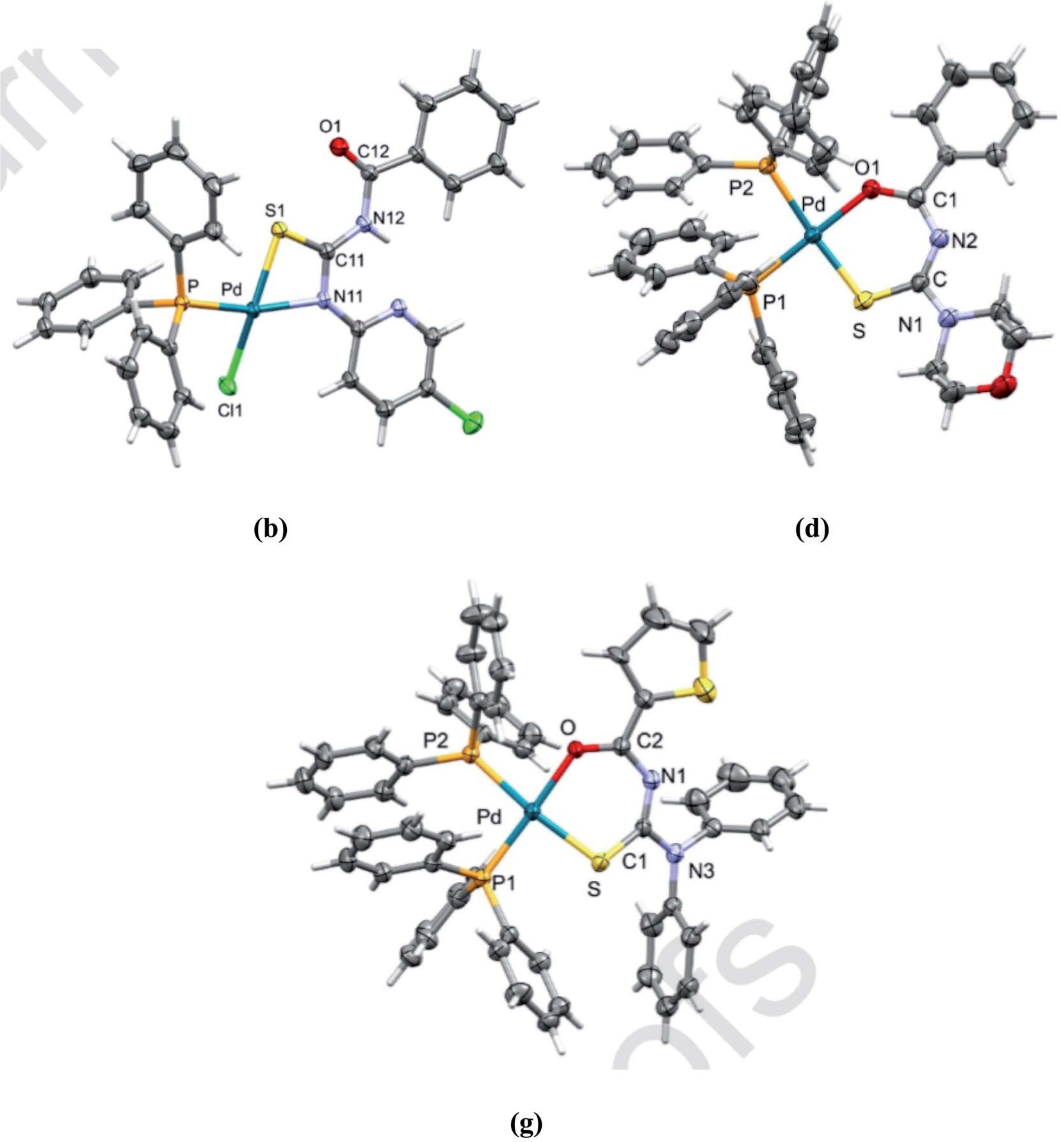
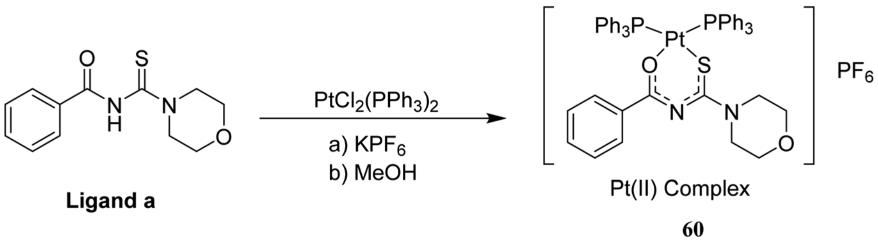


Fig. 13 ORTEP view of the complexes **58(b)**, **59(d)** and **46(g)**, showing 50% probability ellipsoids.

The novel chiral thiourea ligands **79, 80** derived from unprotected D/L-alanine were combined with Ru(II)-*p*-cymene **78** to form Ru(II)-complexes **81** and **82** by Sheeba *et al.*[60] in the same manner as described in Scheme 25. Their structures were confirmed by using spectral and analytical methods. The synthesized compounds catalyzed the asymmetric transfer hydrogenation of ketones to secondary alcohols with high enantiomeric access.



Scheme 17 Synthesis of Pt(II) complexes with thiourea ligand **a**.

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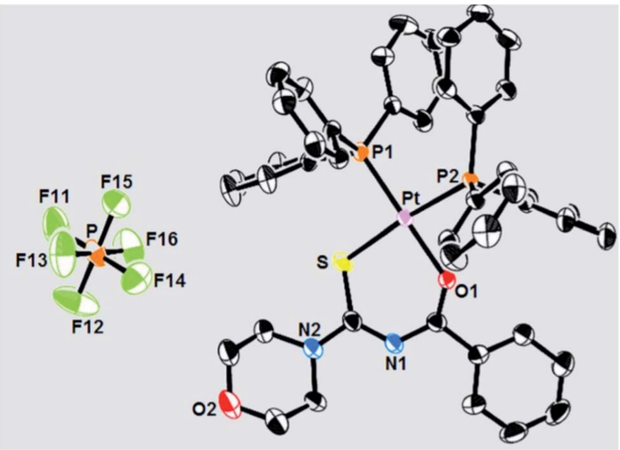

Fig. 14 ORTEP view of the complex **60** showing 30% probability ellipsoids.

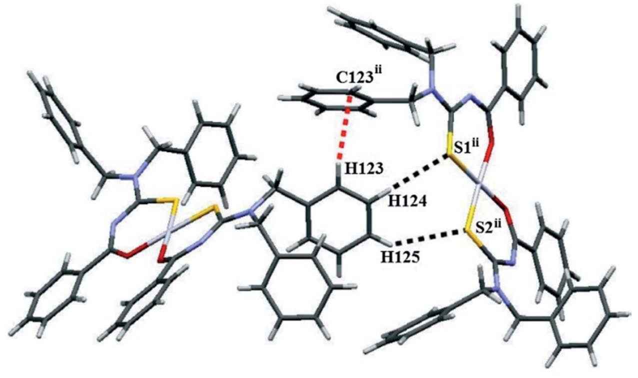

Fig. 16 Molecules in the complex linked by C–H⋯S (black), C–H⋯C(red) and hydrogen bond dashed lines.

6. Applications

6.1 Pharmacological aspects

In last few decades, great interest has been given to the most prominent class of organic compounds that are thioureas. Many articles have been published on the biological activities of 1-(acyl/aroyl)-3-(substituted)thiourea derivatives. Nowadays it's the most mesmerizing area for most scientists, thousands of new derivatives are created by the alteration of structural topographies to get vast biological activities.[19,61] In this section, we will discuss the pharmacological properties of thioureas and their analogs.

6.1.1 Anti-cancer activity. Cancer, being a terminal disease for a long period of time, now has become curable as many compounds have been found to exhibit anti-cancer properties. Thioureas have been found to exhibit antitumor activities having an additional advantage of fewer side-effects.[7]

Pandey and coworkers[62] synthesized two new thiourea derivatives **83a–b** and characterized them. The compounds were tested for their *in vitro* anticancer activities against seven human cancer cells; colorectal (HT29 and HCT116), ovarian carcinoma (A2780, A2780/CP and IGROV-1) and cervical (2008 and C13*) with compound **83(a)** showed significant results against ovarian cancer cell lines and compound **83b** demonstrated good results against cervical and colorectal cancer cells (Scheme 26).

Two other thioureas **84a–b** were synthesized by the condensation reaction between substituted isothiocyanate with diphenylamine by Pandey and coworkers[63] Scheme 27. The synthesized compounds were screened for their anti-cancer

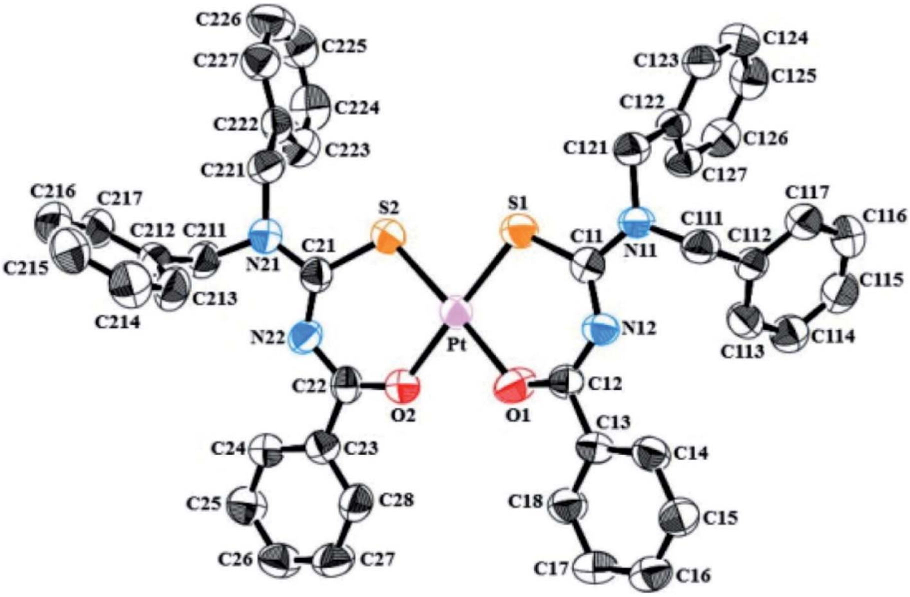

Fig. 15 ORTEP view of the complex showing 50% probability ellipsoids.

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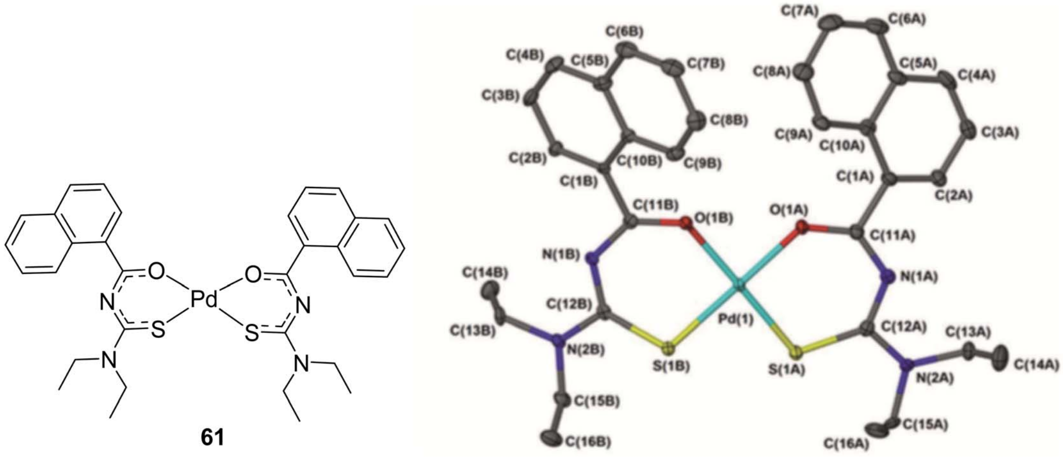
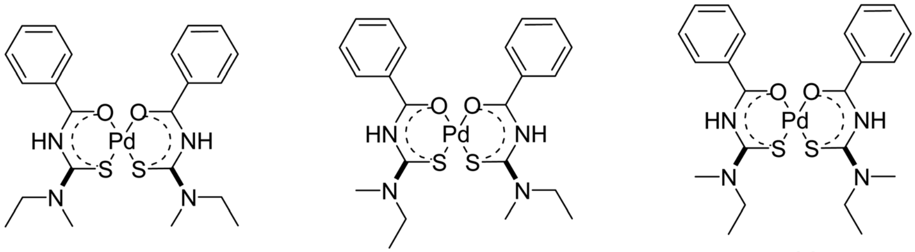


61

Fig. 17 Molecular structure of *cis*-[Pd(L-κS,O)$_2$] **61** from single-crystal X-ray diffraction.



62 **63** **64**

Scheme 18 Structures of *cis*-EE-[Pd(L-κS,O)$_2$], cic-ZE-[Pd(L-κS,O)$_2$], cic-ZZ-[Pd(L-κS,O)$_2$].

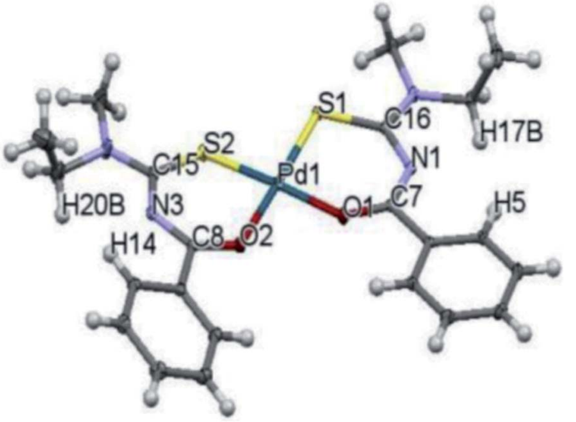


Fig. 18 Molecular structure from single-crystal X-ray diffraction of **62** isomer of *cis*-bis(*N*,*N*-methyl-ethyl-*N*′-benzoylthioureato)–palladium(II).

activities against five human cancer cell lines: ovarian carcinoma (A2780, A2780/CP and IGROV-1) and cervical (2008 and C13*). Both compounds have shown cytotoxic activities against IGROV-1 and cervical cancer cells compared to the other two. The IC$_{50}$ values showed that thiourea **84b** is more potent than **84a** which may be attributed to the presence of Cl group at the *para* position of phenyl group, thus strong electronegative group at *para* position enhanced the lipophilicity and is the reason of increased cytotoxicity.

In another paper in 2020 Pandey *et al.*[64] reported a new series of four thiourea compounds **85a–d** compounds (Scheme 28) and their structures were confirmed by spectroscopic and single-crystal X-ray studies. Hirshfeld analysis and associated 2D fingerprint plots showed their intermolecular connections. The prepared compounds were screened for cytotoxic activities against seven human cancer cell lines, among them **85b** and **85d** demonstrated strong activities than other two compounds which again is due to the presence of strong electron-withdrawing groups (nitro and chloro) at the phenyl ring which are responsible for strong lipophilicity and cytotoxicity of compounds.

Five new ruthenium complexes **88** were synthesized by Oliveira *et al.*[65] Using three different *N*–*N*-disubstituted acyl thiourea ligands **87** and two different diphenylphosphine ligands namely dppe and dppb **86** Scheme 29. All six complexes showed cytotoxic activity against lungs and breast tumor cells and caused alterations in their structures to inhibit the migration of cells, induce cell cycle in the Sub-G1 phase, and cell death by apoptosis. The compounds **88** showed higher selectivity indexes for breast cancer cells for the complex with dppb ligand. Complex **88c**, and **88f** cause structural alterations in the triple-negative breast cancer.

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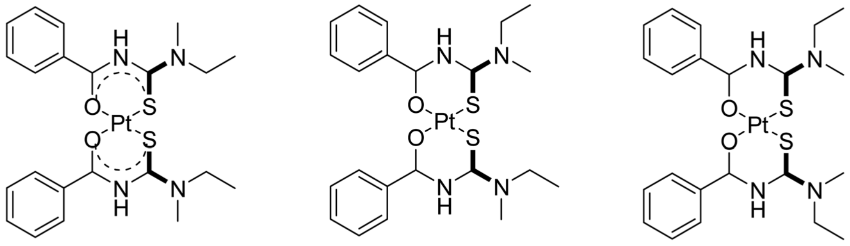
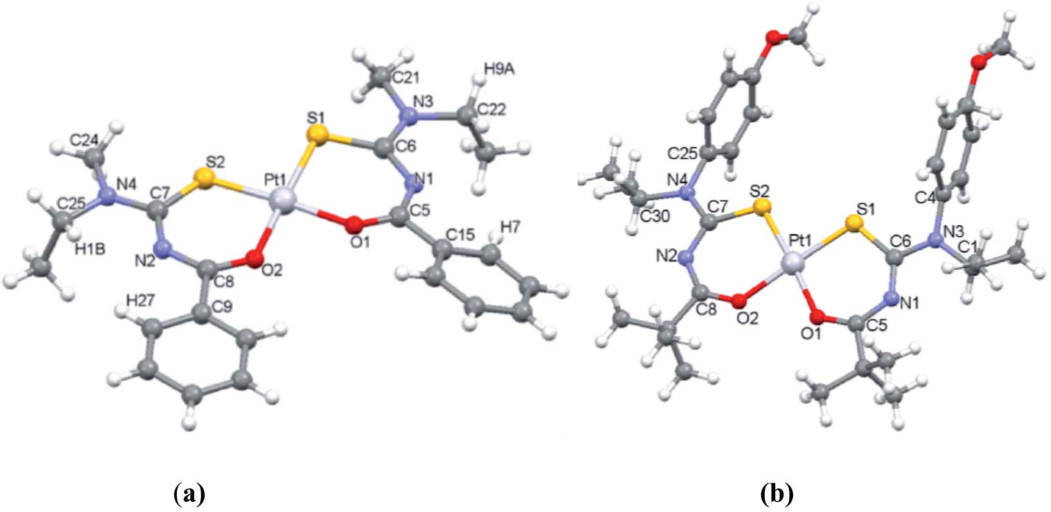


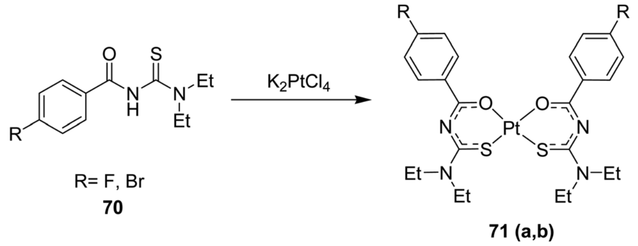
Scheme 19 Structures of *cis*-ZZ-[Pt(L-κS,O)$_2$], *cis*-ZE-[Pt(L-κS,O)$_2$], cic-EE-[Pt(L-κS,O)$_2$].



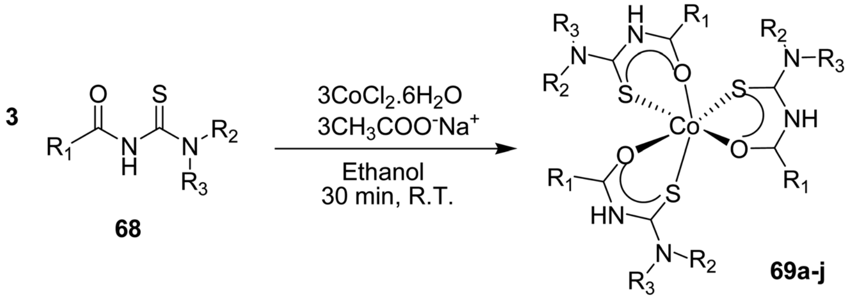
(a) (b)

Fig. 19 Molecular structures from single-crystal X-ray diffraction of (a) **67** and (b) **65**.

Acyl thiourea derivatives **89a–b** attached to histone deacetylase inhibitors were synthesized and characterized by Amily *et al.*[66] These compounds act as ligands toward zinc cation *via* the thiourea binding group and the complexes showed growth inhibition of human colon adenocarcinoma that have lower toxic effects on normal breast cells. Their mode of binding and effects has been studied by using docking studies and the results demonstrated them as good histone deacetylase inhibitors. Both the compounds exhibited good inhibitory potential against cancer cells greater than the normal cells. Compound



Scheme 21 Synthesis of Pt complexes **71a, b**.



Scheme 20 Synthesis of cobalt complexes **69a–j**.

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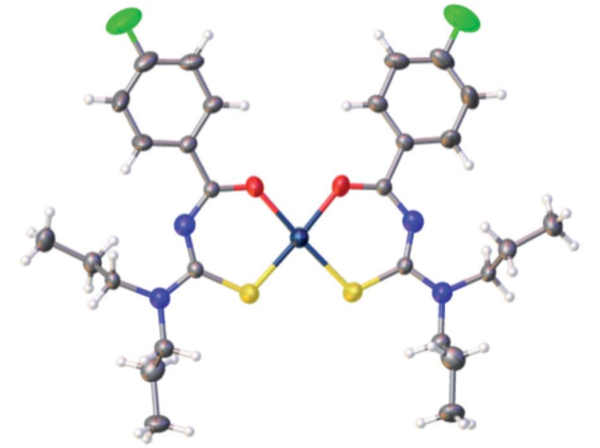


Fig. 20 Molecular structure of complex **71a**.

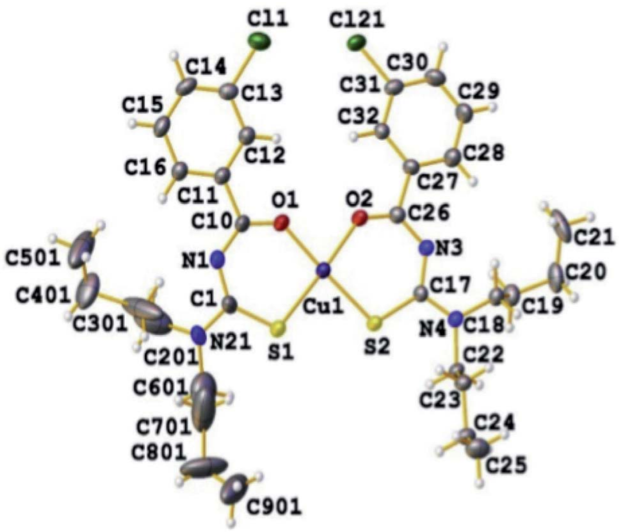


Fig. 21 Molecular structure of bis(*N*,*N*-di-*n*-buthyl-*N*,-3-chlorobenzoilthioureato) copper(II) complex **73d**.

89b was found to be more active than **89a** against HC-04 cell with IC_{50} values 21.44 μM and 24.12 μM (Scheme 30).

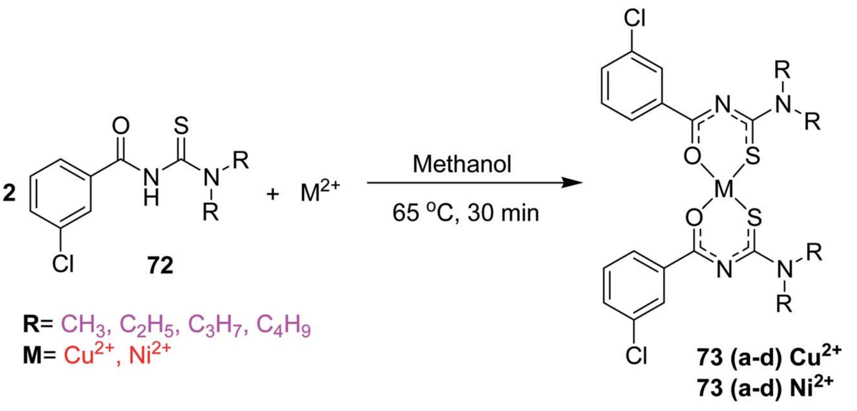
Koca *et al.*[67] prepared new pyrazolyl acyl thioureas containing sulfa drug molecules **90**, the molecular docking studies were performed to confirm the bonding interactions and the results revealed that these compounds exhibit potential anti-cancer properties (Scheme 31).

6.1.2 Anti-fungal agents.

Thioureas have been found to exhibit potential anti-fungal activities,[11] that's why these compounds are preferred because of their additional less toxic nature to the administered systems. The antifungal property is due to the presence of oxygen, sulfur, and nitrogen donor atoms which offers a number of reactive sites granting inhibitory effects against fungal strains.[68]

Asghar and coworkers[69] synthesized a series of ferrocene-based thioureas **91a–i** and characterized them by spectroscopic techniques. It was found that the incorporation of the ferrocenyl group into thioureas is responsible for their enhanced lipophilic character. Compounds were than tested for antifungal activities. The fluoro compounds **91a–c** exhibited more potent activities than chloro and bromo derivatives **91d–i.** In addition, substituent's at *ortho* position in compounds **91a, d, g** were more biologically active than *para* and *meta* substituted compounds which may be attributed to the outstanding effect of an electronegative halo group at *ortho* position than at *para* and *meta* (the inductive effect is valid up to three or four bonds). The electron-withdrawing effect reduces the basicity of N–H and enhances the lipophilic character of the compounds Scheme 32.

Gao and coworkers[70] have synthesized two series of terpene-based acyl thiourea derivatives **92a–j**, **93a–j** (rosin and turpentine derivatives) Scheme 33 to confirm the antifungal activities of naturally occurring products. Using the growth rate method, their inhibitory activities have been assessed. Insertion of acylthiourea unit into terpene framework results in higher antifungal activity and lower toxicity. SAR and QSAR have revealed that electronic and steric effects markedly affect antifungal activities. Among all the compounds **93i** exhibited prominent activity having IC_{50} lower than control drug, all **93a–j** derivatives



Scheme 22 Synthesis of copper and nickel complexes.

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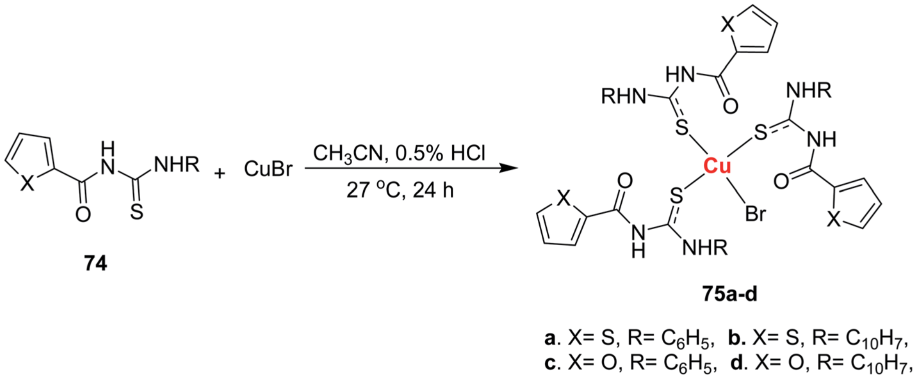


Scheme 23 Synthesis of thiourea copper complexes.

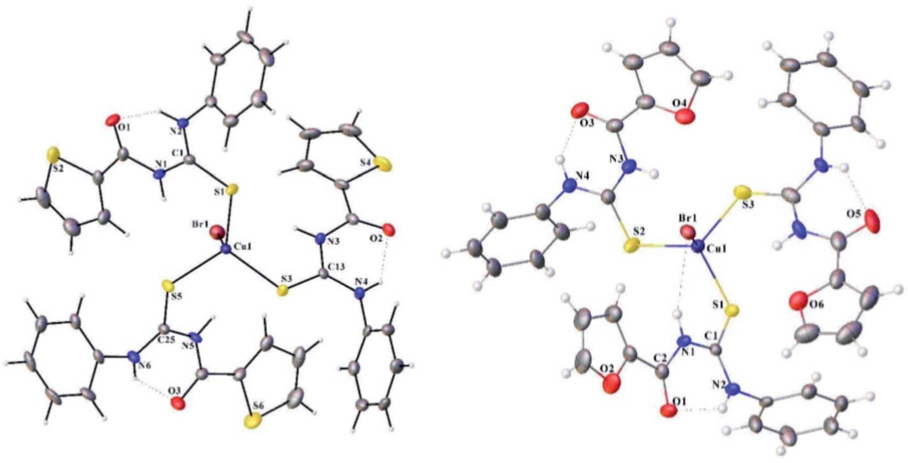
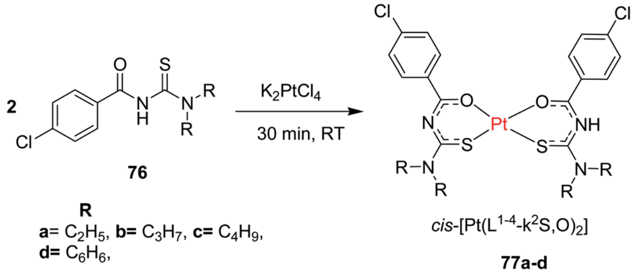


Fig. 22 Molecular structures of complexes 75(a) and (c).



Scheme 24 Synthesis of Pt(II) complexes 77a–d.

showed same antifungal activity compared to control drug carbendazim. Derivatives with electron-donating substituents and aliphatic chains exhibited low antifungal activities, while majority of the compounds in **92a–j** and **93a–j** with electron-withdrawing atoms like F, Cl, Br and $-CF_3$ displayed much higher activities against control drug (**92f–i** > **92c–e** > **92a–b** > **92j**; **93f–i** > **93c–e** > **93a–b** > **93j**). Depending upon the studies, these compounds could be used as replacements for leads and currently used fungicides with less toxic effects.

Rosin-based two series of acyl thiourea derivatives **94a–j**, **95a–n** were designed and synthesized by Wu *et al.*[71] Scheme 34. One of them is thiophene heterocyclic group containing and the other one is without heterocyclic group. Thiophene containing derivatives showed mild to strong anti-fungal activities depending upon the electronic and steric effects and the energy differences indicated by the SAR and QSAR studies. Heterocycle containing derivatives **95a–n** displayed much enhanced anti-fungal activity than **94a–j.** The compounds **95b–e** have similar activities. Studies revealed that electron-withdrawing substituents put more prominent effects than electron-donating groups (**95j**, **95k**, **95l**, **95m** > **95i**, **95n**; **94f**, **94g**, **94h**, **94i** > **94d**, **94e**, **94j**). Thus, these compounds could be used as potential fungicides.

Two thiourea derivatives **96a–b** were prepared and characterized by Ghazal and coworkers[72] Scheme 35. These compounds have shown activities against three strains of fungi. Compound **96a** exhibited strong antifungal activity against *F. soloni* and *A. fumigatus* strains.

6.1.3 Anti-bacterial activity.

The recently synthesized thiourea derivatives have been used in biomedical fields and a large number of these compounds have anti-bacterial properties associated with them.[6,73,74]

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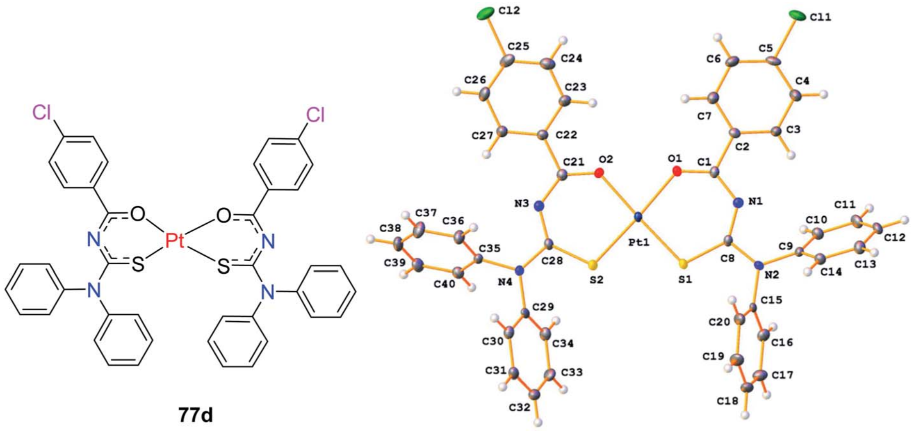
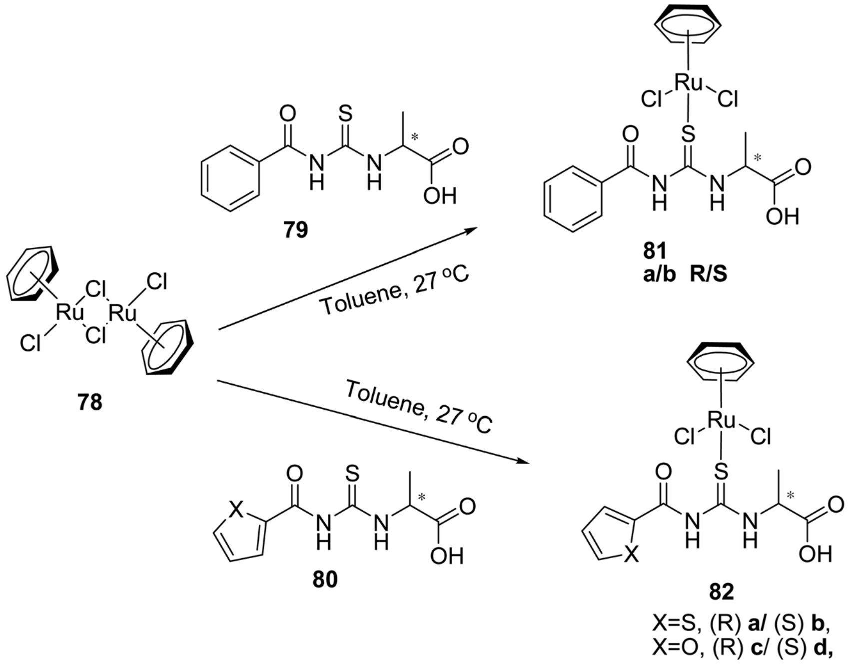


Fig. 23 Molecular structure of **77d**.



Scheme 25 Synthesis of complexes **81** and **82**.

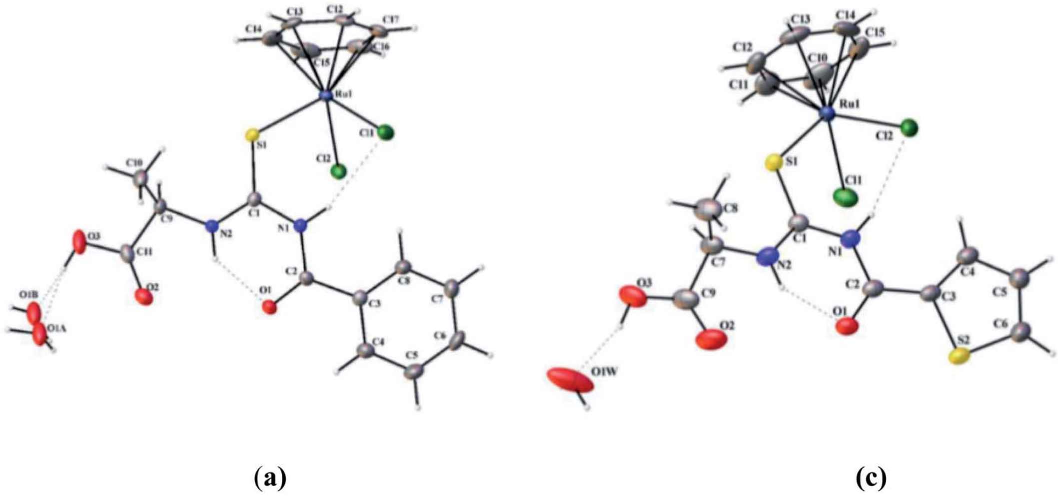


Fig. 24 Thermal ellipsoidal plot (50% probability level) of compound **81(a)** and **82(c)**.

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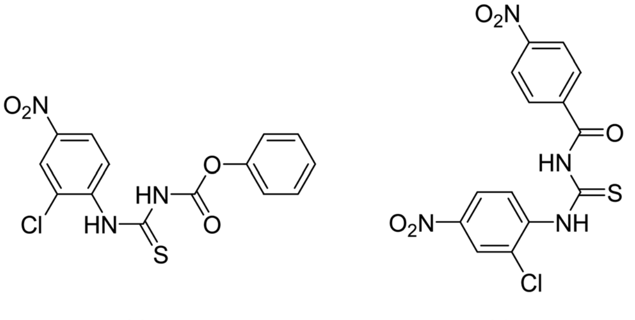
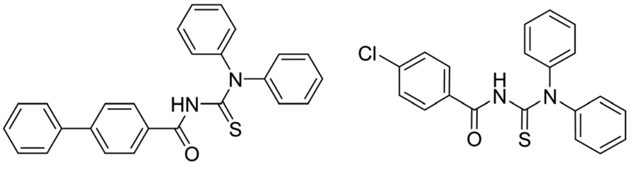


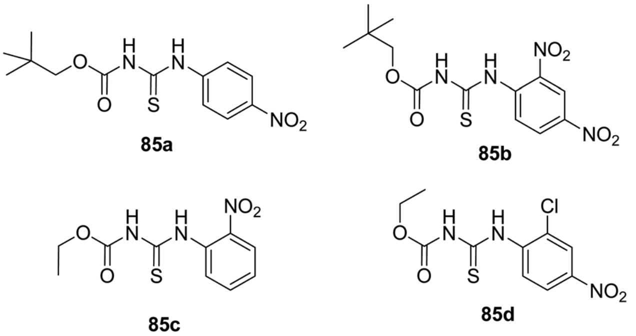
83a **83b**

Scheme 26 Structures of **83a–b** thioureas.



84a **84b**

Scheme 27 Thiocarbamides **84a–b**.



85a **85b** **85c** **85d**

Scheme 28 Structures of **85a–d**.

El-Gaby *et al.*[75] synthesized two series of sulfonamide acyl-thiourea derivatives **97a–e**, and **98a–e** by using the ethyl carbamate and *N*-substituted 4-aminobenzene sulfonamide derivatives Scheme 36. The *in vitro* antibacterial activities of the compounds were tested for four Gram-positive bacteria namely *Streptococcus pyogenes*, *Bacillus subtillis*, methicillin-resistant *Staphylococcus aureus*, and *Staphylococcus aureus*, and three Gram-negative bacteria. The results indicated that compounds **98b** and **97d** displayed significant activities against both Gram-positive and Gram-negative bacteria, then **98a**, **98c**, and **98e**. Compound **97d** was found to be sensitive one. Different studies have referred towards their anti-bacterial activities and the final products involving these acyl-thiourea derivatives are useful in molecular docking studies.

A series of thioureas **99a–e** using 4-nitro-2-cyano aniline with different carboxylic acids as starting materials was synthesized by Saeed *et al.*[76] Scheme 37. All these compounds were obtained in very good yields and were evaluated for antibacterial, antifungal, and α-amylase activity. The compounds were tested against *Enterobacter aerogenes*, *Escherichia coli*, *Micrococcus luteus*, and *Staphylococcus aureus* bacterial strains. All compounds **99a–e** displayed good to prominent antibacterial activity compared to standard drug kanamycin. Compound **99e** was more potent among all and displayed very prominent activity in the series, which may be attributed to the presence of two aryl groups connected with thiourea part. Compound **99d** exhibited low activity against bacterial strains because it contains acetyl attached with thiourea. Their molecular docking studies were also carried out to explain the enzyme inhibition activity.

A new series of thiourea and guanidine derivatives **100a–j** were prepared by Saeed and coworkers.[77] The compounds **100a–j** were tested for antibacterial activity against Gram-positive, Gram-negative, and several isolates from patients with cystic fibrosis. The compound **100g** showed good antibacterial activity against tested bacterial strains. The activities exhibited by several derivatives, highlight the importance of halo-phenyl group in the guanidine moiety Scheme 38.

Maalik *et al.*[78] prepared a series of new 1-benzoyl, 3-phenylthiourea derivatives **101a–j** with systematic substitution on the phenyl ring and evaluated their biological activity as antibacterial compounds to find their importance in the medicinal field Scheme 39. The research group evaluated the prepared compounds using molecular docking studies. Antibacterial activity was carried out against ten bacterial strains, according to the findings, compounds **101(a, c** and **i)** with –Cl, and –OMe substituents displayed prominent activity against all bacterial strains, whereas rest of the derivatives exhibited moderate or no activity, these findings are confirmed the previous papers that halo and methoxy groups on aryl ring displayed excellent antibacterial activities.

Similar halo-benzoyl thiourea derivatives with more than one fluorine atom and trifluoromethyl group as substituents were prepared and characterized by Limban *et al.*[79] Scheme 40. The information from molecular docking studies had shown their affinity to bond with *E. coli* DNA and have exceptional antimicrobial activity. The compounds with fluorine atoms exhibited the best anti-bacterial effects whereas those with more than one fluorine atoms had shown antifungal activity. The compound **102a** showed the highest spectrum of antibacterial activity, being active against both Gram-positive and negative bacteria which may be attributed to the presence of fluorine on the phenyl ring. Multiple fluorine atoms in the derivatives **102(b, c, d** and **e)** did not affect the antibacterial activity. The compounds with trifluoromethyl group **101e** and **102g** were active on *E. coli*.

6.1.4 Antituberculosis agents.

Tuberculosis and the propagation of multi-drug-resistant tuberculosis strains nowadays is a serious health issue that enables many scientists for the development of new drugs for the cure of tuberculosis.[80] Thioacetazone antibiotic and its more recent generation SRI-224 contains the same isoxyl like pharmacophore, the thiourea and is responsible to inhibit the synthesis of mycolic acid.[81]

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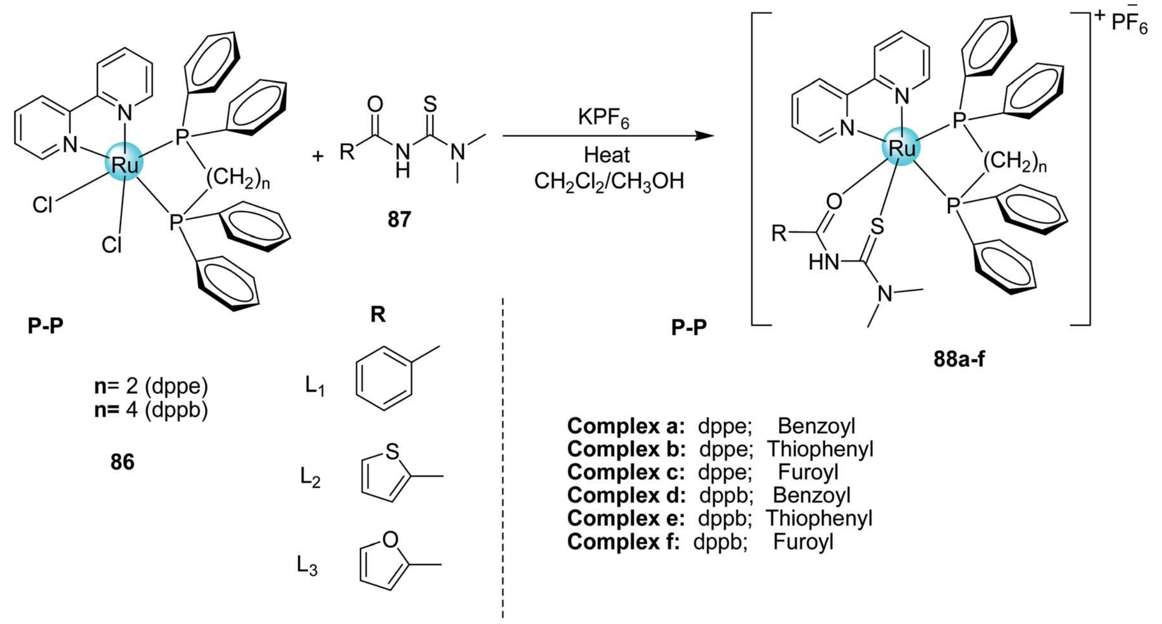
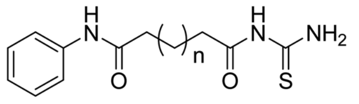
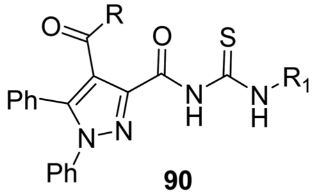


Scheme 29 Synthesis of Ruthenium complexes **88a–f**.



89
n =2 (a)
n= 3 (b)

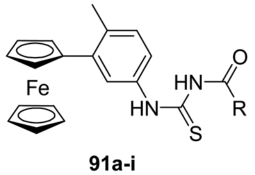
Scheme 30 Acyl thioureas with zinc binding groups.



90

Scheme 31 Pyrazol acylthioureas.

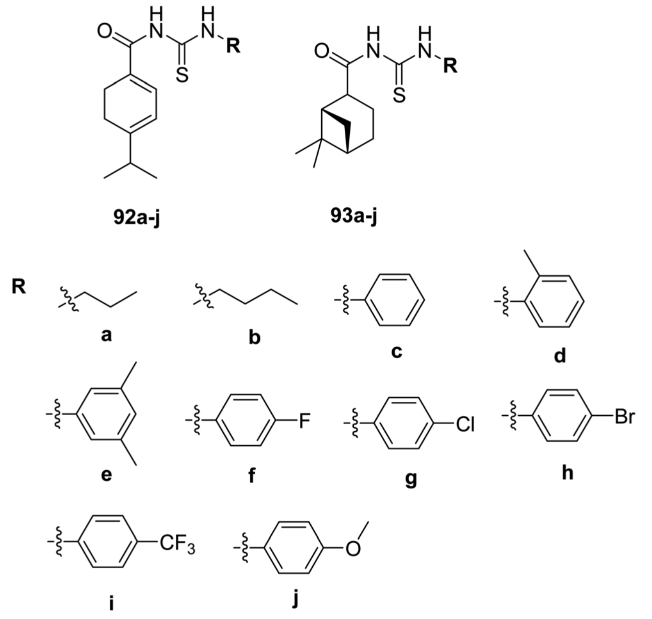
a	**2-FC$_6$H$_4$**	**f**	**4-ClC$_6$H$_4$**
b	**3-FC$_6$H$_4$**	**g**	**2-BrC$_6$H$_4$**
c	**4-FC$_6$H$_4$**	**h**	**3-BrC$_6$H$_4$**
d	**2-ClC$_6$H$_4$**	**i**	**4-BrC$_6$H$_4$**
e	**3-ClC$_6$H$_4$**		



91a-i

Scheme 32 Ferrocene-based thioureas.

Noroc *et al.*[82] designed and prepared three new *N*-(2-phenethylbenzoyl) thioureas **103–105** Scheme 41. The synthesized compounds were tested on both clinical and standard isolated strains of *Mycobacterium tuberculosis* and the acute toxicity and minimum inhibitory amounts were checked in this study. All the compounds have no toxicity in acute tests and are promising derivatives for the design of medicines for the treatment of tuberculosis. The phenethyl group in the derivatives was utilized as bioisoster of the isopentyl group and halogens were incorporated to enhance the lipophilicity. The results revealed that all **103–105** derivatives showed no toxicity in mice and tuberculostatic effects with a lower concentration of 10 μg mL^{-1} on both strains of *Mycobacterium tuberculosis* were seen. The



Scheme 33 Terpene based acyl thioureas.

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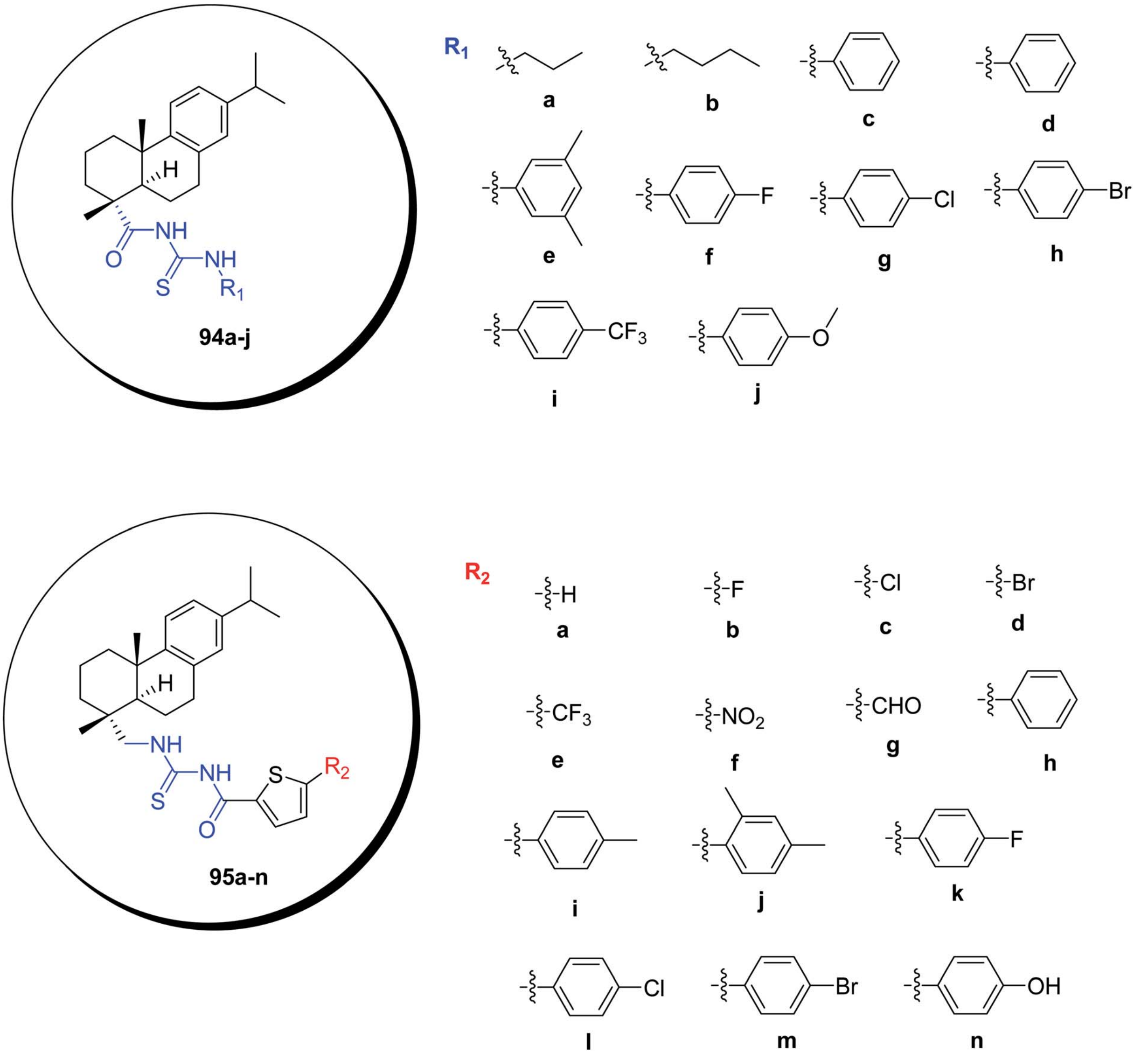
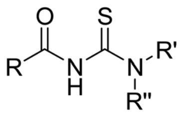


Scheme 34 Synthesis of dehydroabietyl acyl thioureas.



96a-b

a. R= *n*-Bu; R'= Me; R''= Ph;
b. R= *n*-Bu; R'= Ph; R''= Ph;

Scheme 35 Thiourea derivatives 96a–b.

halo substitutions and their position have little effect on tuberculostatic effect.

6.1.5 **Antidiabetic activities.** Nowadays, diabetes mellitus type-2 is the most chronic death causing disease all over the world. WHO reports[83a] revealed that diabetes will be the seventh disease causing deaths across the world. To treat diabetic patients, control of postprandial glucose is necessary which can be achieved by inhibition of α-glucosidase enzyme that is located on the brush border surface of the small intestine. The α-glucosidase enzyme lowers the glucose level obtained from dietary complex carbohydrate by reducing the absorption of glucose into the blood and decrease the plasma glucose,[83b] thioureas also inhibit the α-glucosidase enzyme.

Patujo *et al.*[84] synthesized a new series of bisferrocenylbisthiourea derivatives **106a–e** in good yields Scheme 42 and evaluated their antidiabetic activities to check the pharmacological strength of the prepared compounds. For this purpose, the compounds **106a–e** were explored for the enzyme scavenging potential against enzyme alpha-amylase. The results revealed that derivatives **106(e, b, c, a)** showed scavenging potential having IC_{50} values, 22.8, 209.2, 112.0 and 251.5 μg m^{-1}, showing only **106a** active inhibitor of enzyme. The derivatives were then tested for scavenging potential against α-

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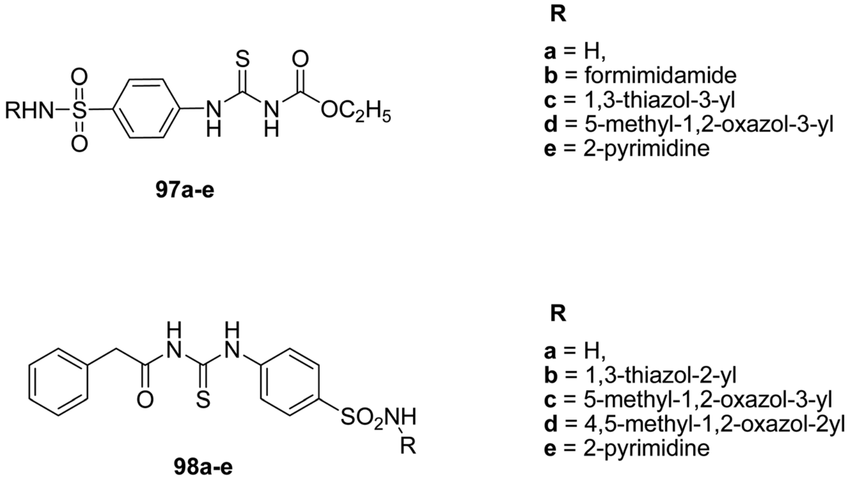


97a-e

R

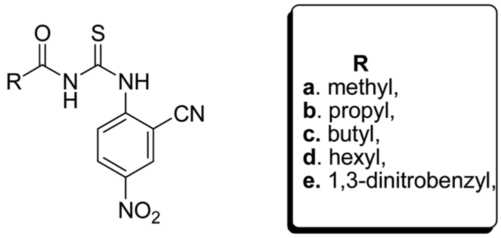
a = H,
b = formimidamide
c = 1,3-thiazol-3-yl
d = 5-methyl-1,2-oxazol-3-yl
e = 2-pyrimidine

98a-e

R

a = H,
b = 1,3-thiazol-2-yl
c = 5-methyl-1,2-oxazol-3-yl
d = 4,5-methyl-1,2-oxazol-2yl
e = 2-pyrimidine

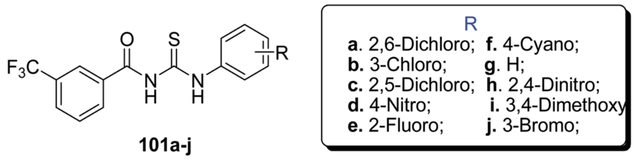
Scheme 36 Thioureas containing sulfonamide.



99a-e

R
a. methyl,
b. propyl,
c. butyl,
d. hexyl,
e. 1,3-dinitrobenzyl,

Scheme 37 Thioureas with different alkyl chains.



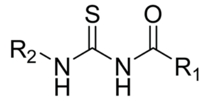
101a-j

R
a. 2,6-Dichloro; **f.** 4-Cyano;
b. 3-Chloro; **g**. H;
c. 2,5-Dichloro; **h**. 2,4-Dinitro;
d. 4-Nitro; **i.** 3,4-Dimethoxy
e. 2-Fluoro; **j.** 3-Bromo;

Scheme 39 Thioureas 101a–j.

glucosidase enzyme. The results indicated that **106(e, d)** inhibit enzyme, and **106e** is much better than **106d** which is due to the presence of ferrocenyl group at different position. Thus, these compounds can be used as potential drugs in the medicinal field.

Rehman and coworkers[85] synthesized a new series of pyridine-2,4,6-tricarbohydrazide thiourea derivatives **107a–i** in good yields (63–92%) Scheme 43. In order to evaluate the pharmacological importance of newly synthesized compounds, they were tested against α- and β-glucosidases enzymes as these enzymes are responsible for treating type-2 diabetes mellitus (T2DM). The results revealed that among all the compounds **107a–i**, derivative **107i** was the more potent in the series with IC_{50} value 25.49 ± 0.67 μM and it was found even more potent than reference drug acarbose having $IC_{50} = 38.22 \pm 0.12$ μM. The SAR studies suggested this activity in **107i** is due to the presence of fluoro group at the C-4 position of aryl ring which offers a suitable environment for interaction with the active site of enzyme. The second active in the series is **107f** (IC_{50} 28.91 ± 0.43 μM), then **107h** (*IC50* = 30.66 ± 0.52 μM), and lastly **107e** (IC_{50} = 35.01 ± 0.45 μM) offers good inhibition against α-glucosidase enzyme (**107i** > **107f** > **107h** > **107e** > **107g** > **107d**). Thus, it can be concluded that halo substitution at the C-4 position delivers good inhibition against the enzyme.



100a-j

R$_1$
a. $C_{10}H_{15}$; **f.** $C_{10}H_{15}$;
b. $C_{10}H_{15}$; **g.** $C_{10}H_{15}$;
c. $C_{10}H_{15}$ **;** **h.** $C_{10}H_7$;
d. $C_{10}H_{15}$; **i**. 2,4-di-Cl-C_6H_3;
e. $C_{10}H_{15}$; **j.** 4-CH_3-C_6H_4;

R$_2$
a. C_6H_{11}; **f.** 2,3-di-Cl-C_6H_3;
b. C_6H_5; **g**. 2-Br-4,6-di-F-C_6H_2;
c.3 -F-4-CH_3-C_6H_3**;** **h.** 2-Br-4,6-di-F-C_6H_2;
d. 2-NO_2-C_6H_4; **i.** 2-Br-4,6-di-F-C_6H_2;
e. 4-CH_3CO-C_6H_4**;** **j.** 2-Br-4,6-di-F-C_6H_2;

Scheme 38 Thiourea compounds 100a–j.

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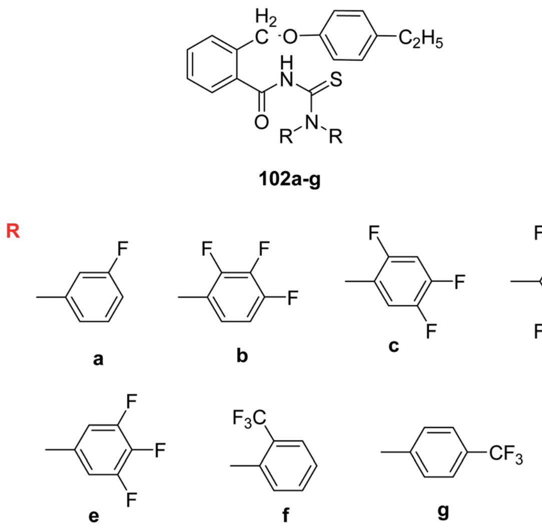
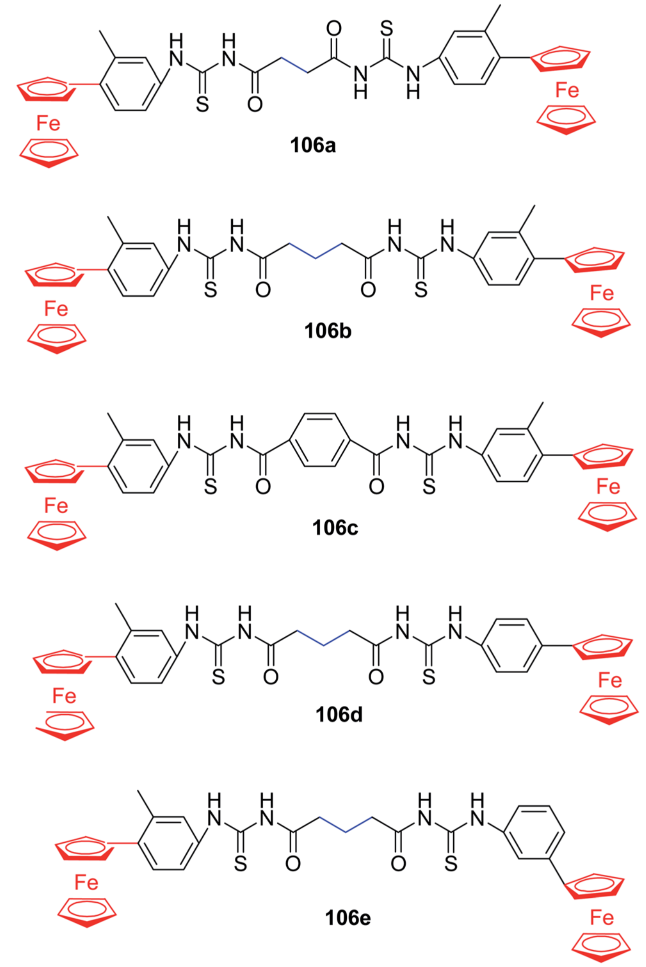


Scheme 40 New benzoyl thiourea derivatives **102a–g**.



Scheme 42 Bisferrocenylbisthioureas**106a–e**.

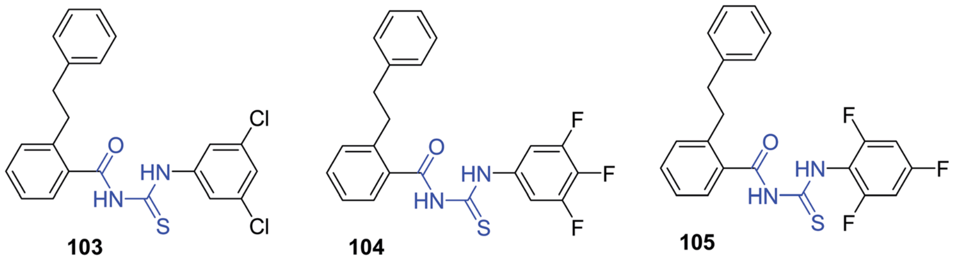
6.1.6 Enzyme inhibitors. Thioureas have also gained importance for their enzyme-inhibition activities, recently developed few enzyme-inhibitors are listed here.

Our research group[86] synthesized a series of 1-acetyl-3-aryl thioureas **108a–o** and characterized them using spectroscopic techniques and X-ray diffraction studies Scheme 44. These compounds were subjected to computational studies and their cholinesterase inhibition activities were evaluated. All these derivatives showed selective inhibition against acetylcholinesterase except **108i** and **108o**. Compound **108b** showed exceptional potent inhibition activity against acetylcholinesterase whereas **108i** has potential activity against butyrylcholinesterase. Molecular docking studies further supported the experimental results. Acetyl cholinesterase inhibitors perform important role in the treatment of Alzheimer's disease.

Saeed and our research group[87] synthesized a series of quinoline-based thiourea derivatives **109a–j** in excellent yields Scheme 45. These thioureas were evaluated to be efficient in radical scavenging activities and in tyrosinase inhibition. According to docking and kinetic studies, the compound **109c** inhibited the enzyme non-competitively with $IC_{50} = 0.0070 \pm 0.0098$ μM and it could also be identified as potent lead compound to design the effective tyrosinase inhibitors and can be used in food and medicine. Tyrosinase enzyme also play crucial role in melanin biosynthesis and browning of vegetables and fruits.

6.1.7 Drug templates. The structural features of thioureas have enabled us to use them as active component of drugs. These compounds due to less toxicity index and other features are of prime importance.

Our research group[88] designed and synthesized a new series of acyl/aryl thiourea derivatives **110a–j** in good yields Scheme 46 by utilizing the free amino group of sulfadiazine drug. In order to get the medicinal properties of sulfadiazine drug its new



Scheme 41 2-Phenethylbenzoylthiourea derivatives **103–105**.

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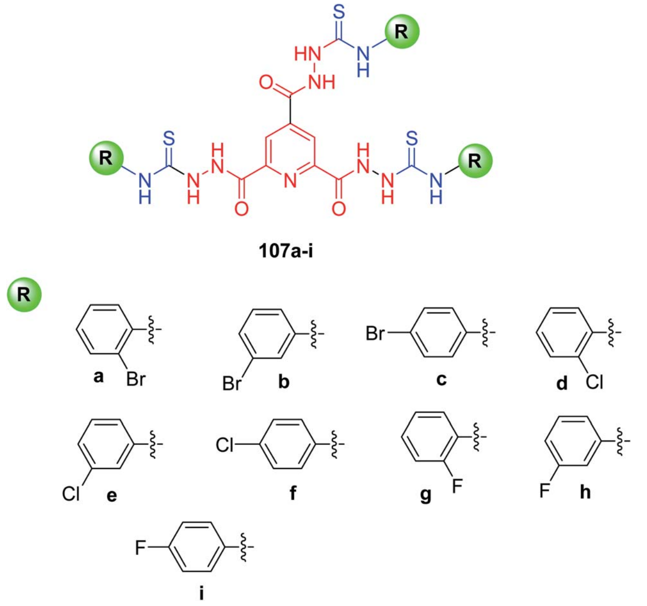
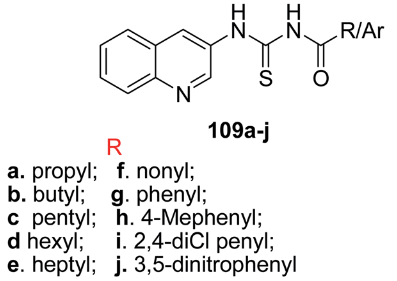


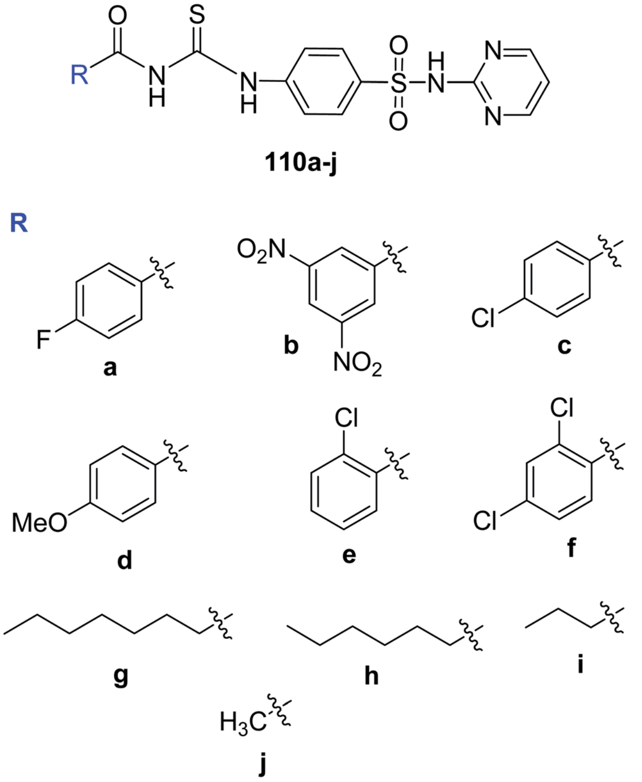
Scheme 43 Pyridine-2,4,6-tricarbohydrazide thiourea derivatives **107a–i**.

derivatives are prepared which have potential medicinal properties. The compounds **110a–j** were tested for calf intestinal alkaline phosphatase (CIAP) activity. All the compounds displayed better inhibition capacity as compared to the reference drug, compound **110c** was found to be active in the series with IC_{50} 0.251 ± 0.012 μM. Their pharmacological studies have shown that all compounds obey Lipinski's rule. They also exhibit lead-like properties with much lesser toxicity. Due to non-mutagenic and irritant behavior, these compounds can be used as drug templates.

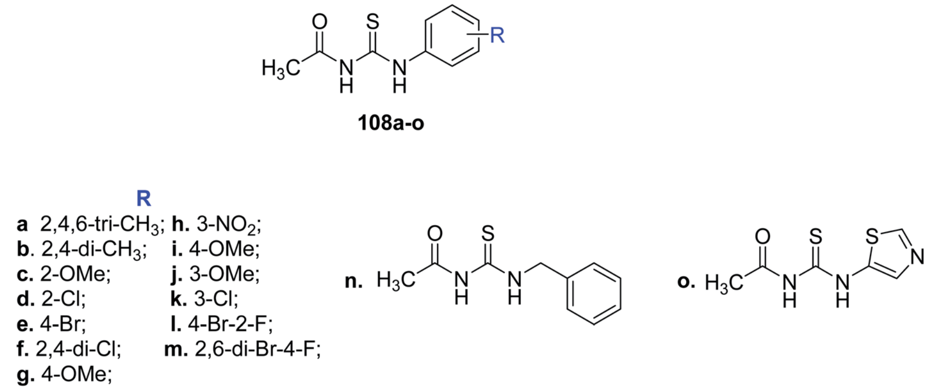
The newly developed 1-heptanoyl-3arylthioureas **111a–i** that can be used as potential inhibitors of urease enzyme were synthesized by our group[89] Scheme 47. These compounds were obtained in very good yield and characterized through spectroscopy and elemental analysis. All the synthesized compounds show drug likeliness according to the Lipinski's



Scheme 45 Quinoline-based thiourea derivatives **109a–j**.



Scheme 46 Thioureas as drug templates.



Scheme 44 1-Acetyl-3-aryl thiourea derivatives **108a–o**.

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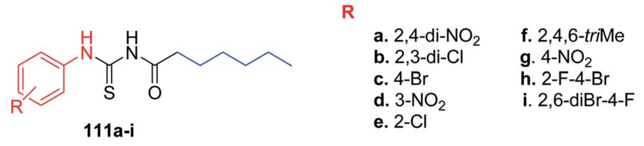


Scheme 47 1-Heptanoyl-3arylthioureas **111a–i**.

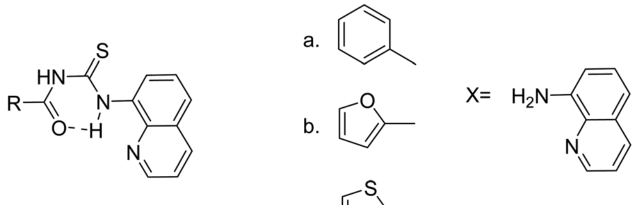
rule. Their kinetic and docking studies confirmed the mode of activity and binding affinity. Especially compounds **111a** and **111c** can act as lead molecules in 4D (drug designing discovery and development).

6.1.8 Bioactive agents. The structural features of thioureas have made them a vital part of various insecticides,[5] antioxidants,[6] and other biomedical agents being synthesized recently by using advanced reactants.

Zhang *et al.*[90] synthesized and characterized a novel series of acyl thiourea derivatives of doramectin **112a–v** Scheme 48. Their biological assay and molecular docking studies showed them to be used as potential insecticides. The presence of hydrogen bond groups in their structures might enhance the insecticidal activity.

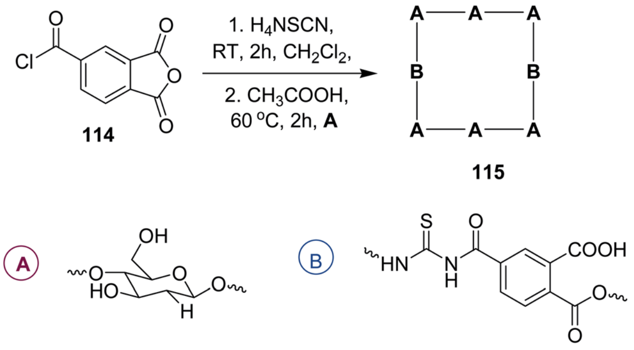
Acyl thiourea derivatives **113a–c** were synthesized and characterized using spectroscopy and elemental analysis by Kalaiyarasi *et al.*[91] Scheme 49. Their molecular structures were also determined, and molecular docking studies showed them to exhibit anti-malarial and anti-inflammatory activities. These compounds also possessed antioxidant activity.

Cross-linked chitosan hydrogels **115** using novel trimellitic anhydride isothiocyanate were synthesized and characterized by spectroscopic techniques by Mohamed *et al.*[92] Scheme 50. Their swell abilities and antimicrobial activities were found to be dependent on the cross-linking moiety contents. It has been found out that chitosan combined with functionalized groups

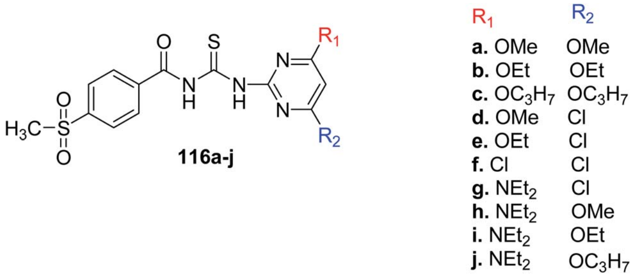


113a-c

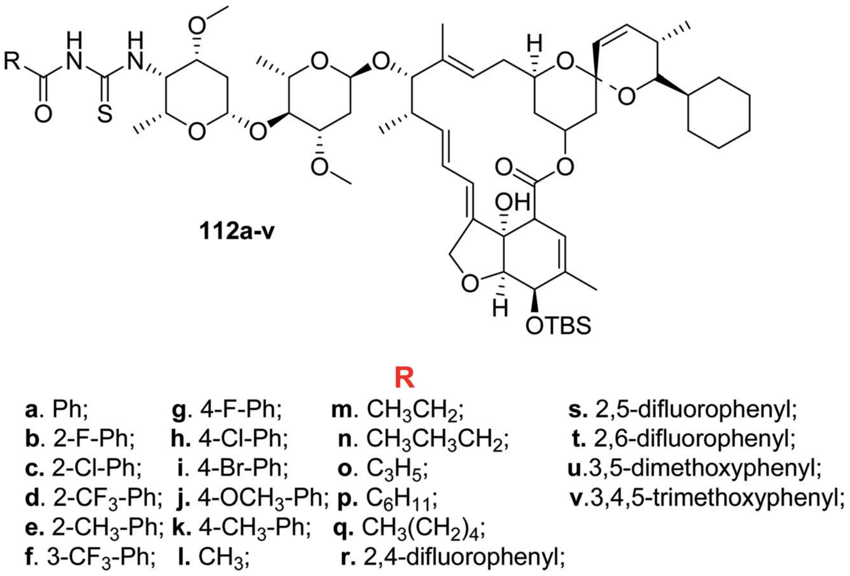
Scheme 49 Thiourea derivatives **113a–c**.



Scheme 50 Cross-linked chitosan hydrogels **115**.



Scheme 51 Thioureas containing substituted pyrimidines **116a–j**.



Scheme 48 Thiourea derivatives of doramectin.

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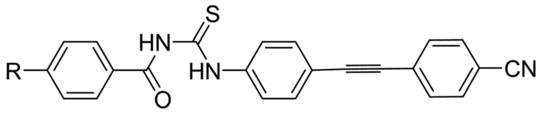


117a-b

R= C_2H_5 (**a**) CH_3 (**b**)

Scheme 52 Thioureas for CO_2 sensing.

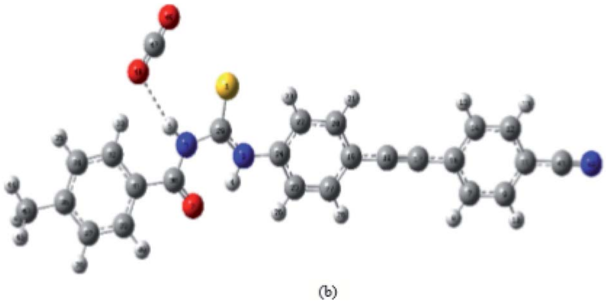
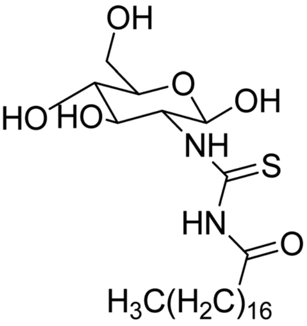


Fig. 25 Structures of **112b** and its interaction with CO_2 analyte.



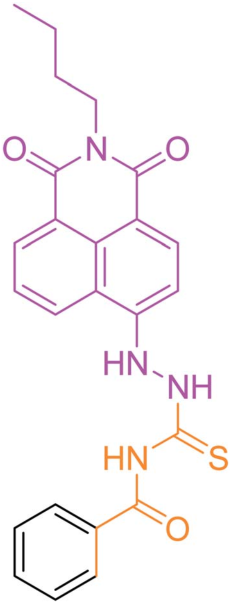
118

Scheme 53 Steroyl thiourea derivative **118**.

provided the adequate systems and promising candidates in biomedical fields.

Many strategies have been developed for new bioactive agrochemicals for crop protection, and acyl thiourea derivatives have been reported as attractive compounds in this field.

Li *et al.*[4] synthesized a new series of thioureas containing substituted pyrimidines **116a–j** (Scheme 51). The newly prepared compounds were tested for herbicidal activity, and the preliminary results indicated some derivatives had good activity against *Amaranthus retroflexus*, and *Digitaria adscendens*, particularly compound **116d** and **116f** displayed inhibitory potential on *D. adscendens*. Moreover, compounds **116d** and **116f** had higher comparative herbicidal activity on *Echinochloa crus-galli* than the commercial herbicides. The SAR studies showed that when the spatial volume of pyrimidine substituents is small like (Cl, OMe and Me) these derivatives have higher activities because these can easily fit into the active sites of enzyme.



119

Scheme 54 Thiourea **119**.

6.2 As chemosensors

Several thiourea derivatives have been prepared and used for the naked eye detection of many metal ions, this activity of thiourea is due to the presence of nitrogen, sulfur and oxygen atoms which makes interactions with metal ions.[61]

Carbon dioxide (CO_2) is one of the important greenhouse gas in atmosphere mostly caused by fossil fuels and deforestation, which have quickly enhanced the concentration of CO_2 in earth's atmosphere, causing global warming. Thus, global

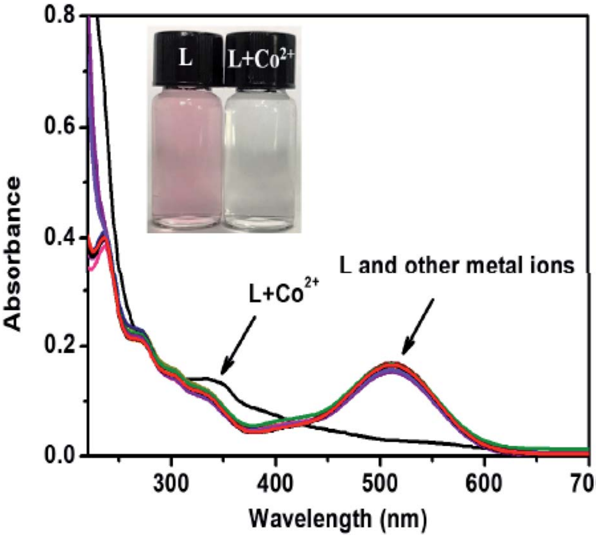


Fig. 26 UV-vis absorption spectra of **119** upon addition of 5 equiv. of salts (Na^+, K^+, Ag^+, Cu^+, Mg^{2+}, Zn^{2+}, Ca^{2+}, Sn^{2+}, Cu^{2+}, Ni^{2+}, Mn^{2+}, Pb^{2+}, Cd^{2+}, Ba^{2+}, Hg^{2+}, Fe^{2+}, Co^{2+}, Fe^{3+}, Al^{3+} and Cr^{3+} in a CH_3CN/HEPES. Colorimetric response of **119** with Co^{2+}.

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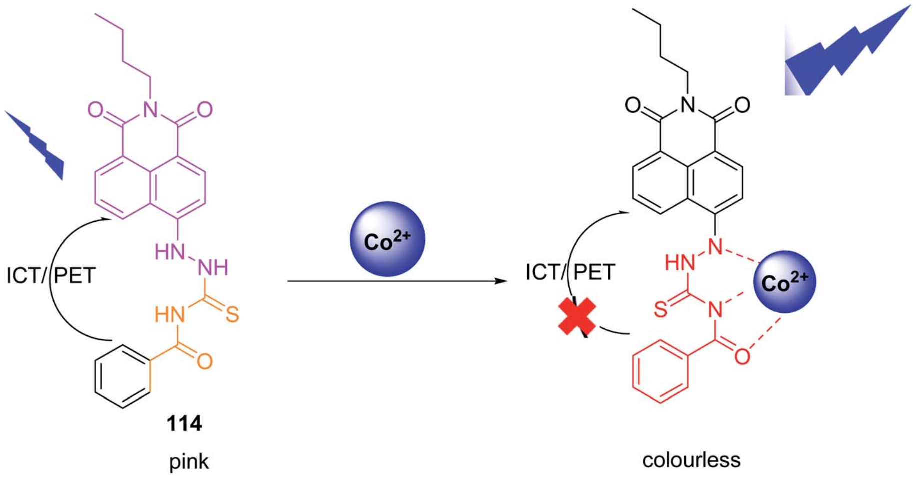

Scheme 55 Sensing mechanism of Co^{2+} by **119** and structure of **119**–Co^{2+} complex.

researchers are developing cheap, low power and miniature in size carbon dioxide sensors with high sensitivity.[93] Daud *et al.*[94] synthesized new ethynylated-thiourea derivatives of 4-ethylbenzoyl-3-(4-ethynylbenzonitrile-phenyl)-thiourea **117a**, and 4-methylbenzoyl-3-(4-ethynylbenzonitrile-phenyl)-thiourea **117b** Scheme 52. These can be used for the detection of CO_2 gas as sensing layers. These sensors do not show any decline in response after recurring usage making them good indicators of significant reproducibility and low relative standard deviation. The sensing capacity is related with the presence of –NH–C═O moiety which makes H-bonding interaction with CO_2 analyte Fig. 25.

A new stearoyl thiourea derivative of chitosan **118** that can be used for the preconcentration of uranium from sulfate solution was synthesized. Its optimal conditions for elution and adsorption have also been studied. The adsorption is an exothermic process and follows a pseudo-first order kinetics. It has a high tolerance towards diverse ions. This method is applicable for uranium determination in various reference samples as reported by Orabi *et al.*[95] (Scheme 53).

Liu *et al.*[96] synthesized a fluorescent chemosensor*N*-(2-(2-butyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[de]isoquinolin-6-yl) hydrazine-1-carbonothioyl)benzamide **119** and characterized it by spectroscopic methods Scheme 54. This chemosensor was designed for the selective detection of Co^{2+} ions Scheme 55. The colour of chemosensor **119** is pink it detected the cobalt ions by a colour change from original pink to colourless and also a significant increase of the fluorescence intensity in CH_3CN solution. This chemosensor is much effective in that it detects the Co^{2+} ions to a lower concentration of 0.26 μM. The analysis

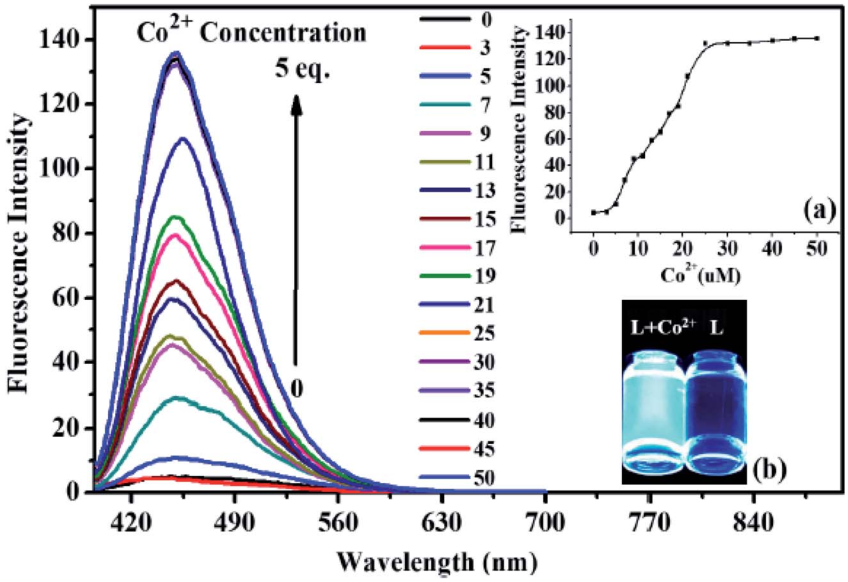

Fig. 27 Fluorescence spectra of **119** (1×10^{-5} mol L^{-1}, $\lambda_{ex} = 380$ nm) after the amounts of Co^{2+} from 0–5 equiv. in CH_3CN/HEPES at Rt. (a) fluorescence titration curve (b) the color change of complex by UV light of **119** and on addition of cobalt ion (5 equiv.) pH = 7.

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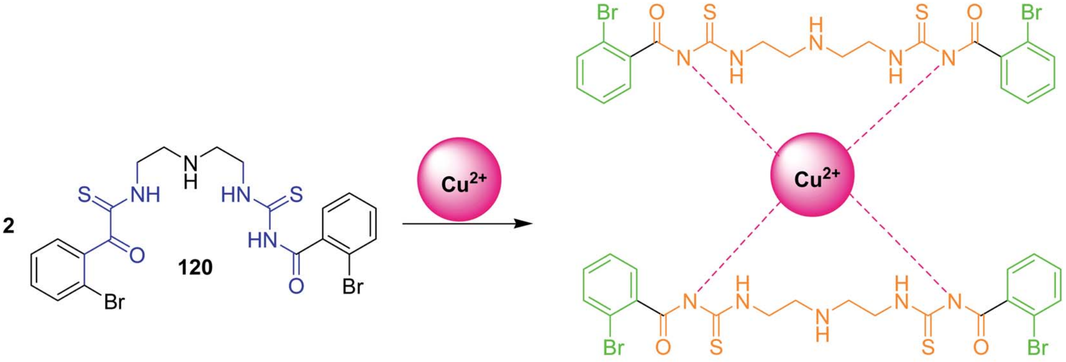

120-Cu^{2+} complex

Scheme 56 Sensor **120** and its complex with Cu^{2+}.

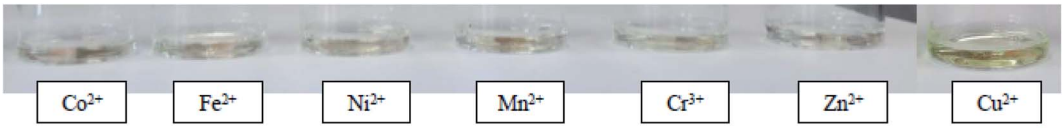

Fig. 28 Colour change by addition of several ions to the sensor **120** free sensor, Co^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Cr^{3+}, Zn^{2+}, Cu^{2+} (left to right).

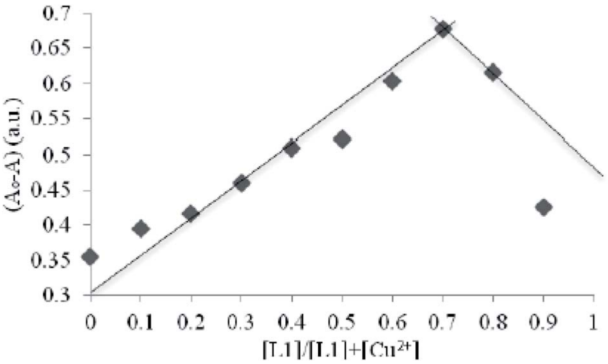

Fig. 29 Job's plot to confirm the ratio of sensor and copper ions 2 : 1.

of Co^{2+} ions can be achieved *via* colour change and spectral behavior. Fig. 26 shows the selectivity of the sensor in many existing ions, pink color and a sharp peak at 510 nm is due to intramolecular charge transfer (ICT) transitions by adding 5 equivalents of cobalt ions this band vanish because of sensor and Co^{2+} complex (Scheme 55) and cause color change from pink to colourless which can be easily seen by naked eye. It is realized that **119** emits weak fluorescence due to a phenomenon called photo induced electron transfer (PET) from the imino nitrogen to the naphthalimide. Fig. 27 shows the fluorescence titration of **119** with cobalt ions, upon titration with cobalt ions, the intensity of fluorescence spectrum increases up to 3 equiv. of cobalt ion and then no change recorded up to 5 equiv. of cobalt ions at 450 nm. The sensor was only selective for Co^{2+} in a large number of other metal ions. Moreover, chemosensor **119** can be used as fluorescent sensor for detecting the Co^{2+} in various biological systems which shows its low toxicity to organisms and better cell permeability in living cells.

Hamedan *et al.*[97] synthesized symmetrical benzoyl thiourea derivative **120** and used it as a colorimetric sensor for the naked-eye detection of Cu^{2+} ions. This sensor like the previous example displayed selectivity towards Cu^{2+} ions in ACN/H_2O binary solutions, thus benzoylthiourea **120** plays a vital role in colorimetric recognition. Studies indicated that sensor **120** recognized the Cu^{2+} ions by creating a stable 2 : 1 sensor-Cu^{2+} complex as shown in Scheme 56. When Cu^{2+} was added to sensor, colour change occurred from yellow to green while the presence of other cations such as Co^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Cr^{3+}, Zn^{2+} did not interfere in the detection process Fig. 28. In addition, the sensor detection limit for the Cu^{2+} was 1.15×10^{-5} M. Job's plot studies Fig. 29 indicated the complex formation and colour change between sensor **120**–Cu^{2+} in 2 : 1 stable ratio. The detection process was monitored by the IR spectra titration method. The results revealed that when sensor formed a complex with Cu^{2+} the C=O absorption peak shifted to higher while thiourea C=S peak remains same which indicated that sensor formed complex with Cu^{2+} through Cu^{2+}–N bond which is near to carbonyl as in Scheme 56 that's why carbonyl absorption peak shifted to a higher number.

6.3. Heterogenous catalysts

Due to efficient hydrogen-bond donating ability, thioureas have been used as organic ligands in the metal–organic frameworks (MOFs) that serve the purpose of heterogenous catalyst.[98] These kinds of catalysts ensure the efficient conversion of desired

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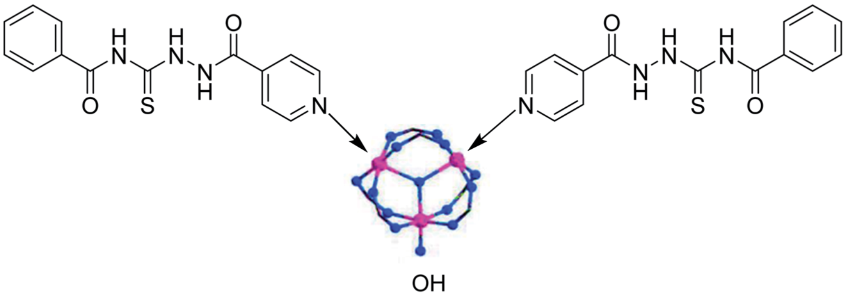

121

Scheme 57 Thiourea-grafted MIL-101(Cr) **121**.

compounds into high-value-added chemicals without any solvent, extreme conditions and even co-catalyst.[99]

Mohammadian *et al.*[100] changed a thiourea-bearing metal–organic framework (MOF) by the introduction of post-synthetic modification done by the complexation of MIL-101(Cr) with pyridine containing thiourea ligand **121** Scheme 57. The research group prepared three different thiourea ligands but the most efficient catalyst was found to be **121** with higher yields. The resultant complex acted as a heterogenous catalyst which prevents the hydrogen bond donating (HBD) organocatalyst to undergo a self-quenching phenomenon. Hence, improving the overall activity of the catalyst. The complexation of MIL-101(Cr) and pyridine bearing thioureas resulted in an activity better to that of parent MOF or ligand performing alone in Biginelli reactions and Friedel–Crafts alkylation.

7. Conclusions

The recent advances have proved thioureas to be crucial reagents for organic synthesis. The extensive use of these compounds as modified ligands in metal complex formation as well as bioactive templates in pharmaceuticals is increasing. The structural modifications have enabled them to be incorporated as chemosensors for many cations and molecules as well as assisted in the synthesis of efficient dugs with lower side-effects and toxicity. Long-chain polymer formation and their use as adhesives has increased their importance manifolds. Molecular docking studies have shown the potent activity against different strains of microorganisms. The modifications and advancements in the structures of these scaffolds is an active area of research. We hope that this review is an incentive for any further advancement in the discussed area.

Conflicts of interest

The authors declare no conflict of interest.

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