An important Scaffold :Biheteroaryl-Pyridyl-Thiazole

Review Article

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Abstract : The present review attempts to bring out some important and significant developments of pyridyl-thiazole heterocyclic compounds in pharmaceutical sector, in the world of thiopeptide antibiotics, in the area of luminescence and pyridyl-thiazole as a ligand in coordination chemistry in recent years. The general purpose of this article is to give an exhaustive and clear picture in biheteroaryl , thiazole-pyridyl bond formation as well as its application in the synthesis of natural products, pharmaceuticals, catalyst , ligands and materials. Accordingly, this review aims to systematize the current information in this field and provide some perspectives for possible applications of this important class of coordination compounds.

IndexTerms **- Biheteroaryl , Pyridyl-thiazole , luminescence, cordination , ligand .**

I. Introduction

Biheteroaryls and their homologues , terheteroaryls , oligoheteroaryls and polyheteroaryls , are an important class of organic compounds. The different biheteroaryls are always an important constituent in areas like liquid crystals , polymers, advanced materials, different natural products , ligands and molecules of medicinal interest. In consideration of applications of this biheteroaryls , it is therefore important to note that organic chemists have made extensive efforts to develop new, efficient and straightforward heteroaryl–heteroaryl bond-forming methods with excellent selectivity and high functional group tolerance under mild reaction conditions. Pyridyl-substituted thiazoles are not among the most studied heterocycles. In any case, some interesting applications as pharmaceuticals do exist. Depending on the substitution pattern, they may have fungicidal activity [1] or they may serve as inhibitors of 5-lipogenase. [2] Besides, they have also been used in medicinal chemistry to access bioactive lead molecules and drug candidates.

Trisubstituted and disubstituted 1,3-Thiazoles, linked to aryl or heteroaryl groups, are privileged structural motifs and have applications in different fields, such as materials science on the preparation of liquid crystals [3], molecular switches [4], sen-sors [5] or cosmetic industry (sunscreens). [6,7] From the viewpoint of coordination chemistry, biheteroaryls are diazadiene ligands and should be capable of forming complexes with metal ions. Multidonor heterocyclic ligands containing both nitrogen and sulfur atoms possess versatile coordination ability toward various transition metal ions; as a result, they have attracted considerable interest, particularly in the synthesis and applications of biomimicking and bioactive coordination compounds. [8,9,10] Among the ligands of this kind, electron-rich polyfunctional thiazole, isothiazole and thiadiazole-based derivatives assume an exceptional importance on the construction of metal complexes of different types, in particular valuable organometallic frameworks and functional materials. The highly fluorescent nature of the ligand can be advantageous for the spectroscopic investigation of complex formation and dissociation equilibria

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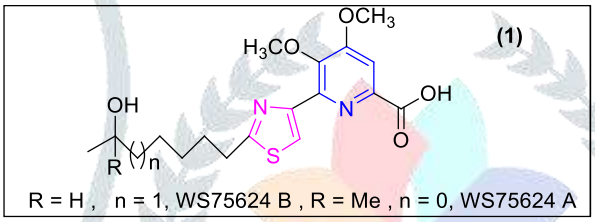
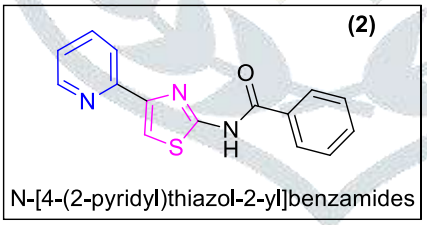
II. Pyridyl-thiazoles - in the medicinal chemistry

The halogen dance reaction using thiazole for the total synthesis of the pyridine-thiazole-containing natural product WS75624 B is suggested by Eric L. Stangeland and Tarek Sammakia [11] which proceeds via the Stille coupling of appropriately functionalized pyridine and thiazole components. WS75624 A and B **(1)** are two related compounds that were isolated from the fermentation broth of *Saccharothrix* sp. No. 75624.[12] These compounds are potent endothelin converting enzyme (ECE) inhibitors and are potential antihypertensive agents. [13] There are two reported syntheses of WS75624 B in the literature, the first by Patt and Massa [14] and the second by Huang and Gordon, [15] and one synthesis of the structurally related molecule WS75624 A.[16]



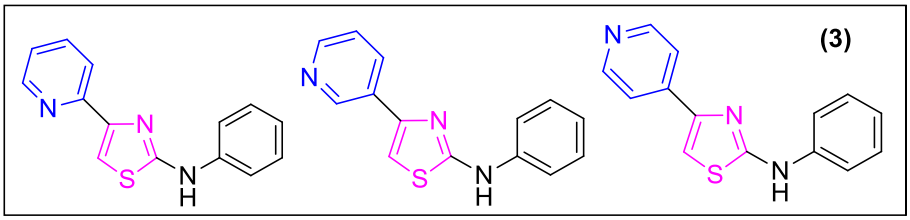
R = H , n = 1, WS75624 B , R = Me , n = 0, WS75624 A

A review of thiazole based heterocycles for bioactive systems [17] described by Someshwar Pola . J. E. M. Koezen et. al.[18] prepared numerous *N*-[4-(2-pyridyl)thiazol-2-yl]benzamides **(2)** , and these compounds exhibited adenosine affinities in the micromolar range .

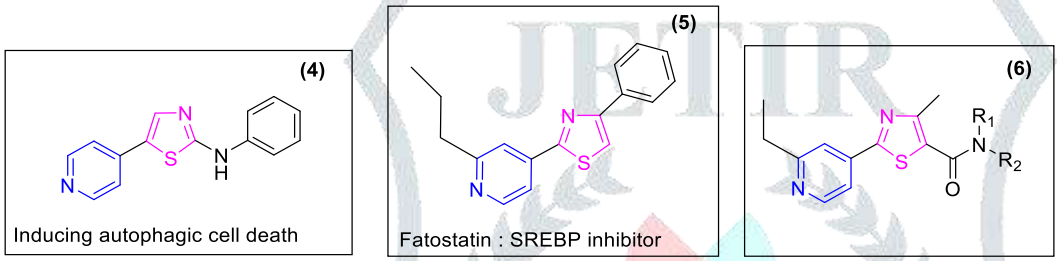


N-[4-(2-pyridyl)thiazol-2-yl]benzamides

Antimycobacterial activity of 2-aminothiazole derivatives **(3)** against Mycobacterium tuberculosis, H37Rv were reported by Parameshwar Makam and Tharanikkarasu Kannan.[19] The reported 2-aminothiazole derivatives contain commonly three aromatic cyclic systems in their structures *viz.* substituted phenyl, thiazole and pyridyl systems. The cell wall permeability , solubility factor were taken into consideration during designing of 2-aminothiazole derivatives, again naphthalene , substituted phenyl rings and positional isomeric pyridyl systems have been incorporated to induce lipophilicity and hydrophilicity likewise.

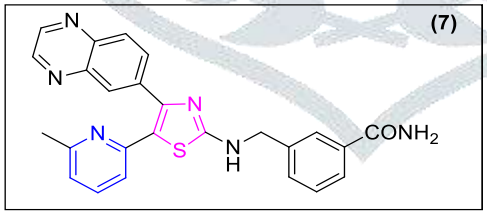


Different biological targets for the antitumor activity involves mainly aryl thiazole.[20,21,22,23] Phenyl-(5-(4-pyridinyl)-2-thiazolyl)-amine **(4)** reported to induce autophagic cell death [24] , Fatostatin **(5)** was reported for metabolic diseases as well as cancer progression through blocking activation of sterol regulatory element-binding proteins (SREBP). [25] The study continued by Wenbo Zhaou et al .[26] for the effects of the series of pyridinyl-thiazolyl carboxamide derivatives **(6)** against angiogenesis through a colony formation assay of human umbilical vein endothelial cells (HUVECs) in vitro.



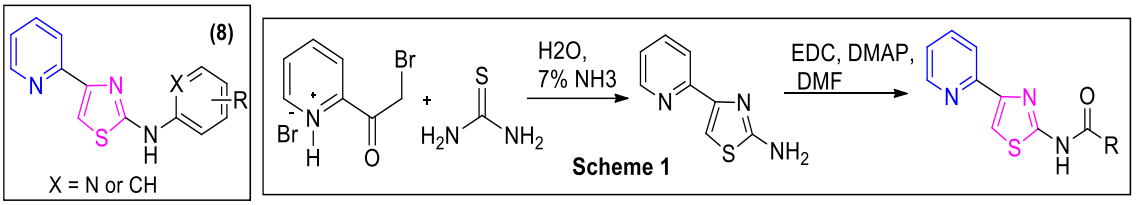
Anticancer agent containing pyridyl thiazole scaffold

Dae-Kee K et al. [27] produced a set of 5-(pyridin-2-yl)thiazoles **(7)** enclosing a *para* or *meta* carboxamide or carbonitrile-substituted phenylmethylamino moiety at the 2-position of the thiazole ring and was estimated for activating receptor-like kinase 5 (ALK5) inhibitory activity in cell-based luciferase publisher assays.



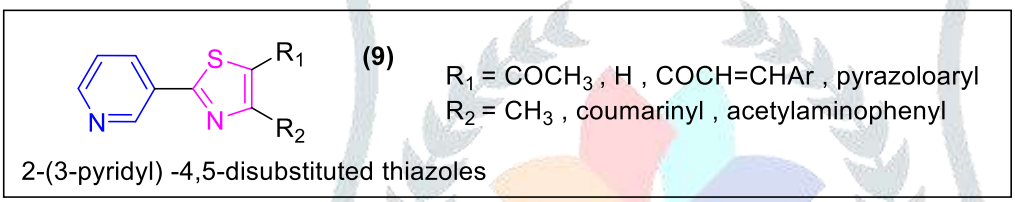
Courtney C. Aldrich et al [28] described the systematic and comprehensive SAR analysis of this aminothiazole scaffold and in vitro drug metabolism studies that resulted in compounds with improved activity profiles over the parent hit compounds. The SAR shows the central thiazole moiety and the 2-pyridyl moiety at C-4 of the thiazole are intolerant to modification. However, the N-2 position of the aminothiazole exhibits high flexibility and successfully improved the antitubercular activity of the initial hit by more than 128-fold through introduction of substituted benzoyl groups at this position. [29,30,31,32,33] Based on this parameters synthesis of N-2-acyl analogues , key bullding block 2-2-amino-4-(pyrid-2-yl) thiazole

(8) was prepared by condensation of 2-bromoacetylpyridine hydrobromide with thiourea **(Scheme 1).** Subsequent coupling of this amine with various aliphatic, aromatic and heteroaromatic acids provided the desired amides.

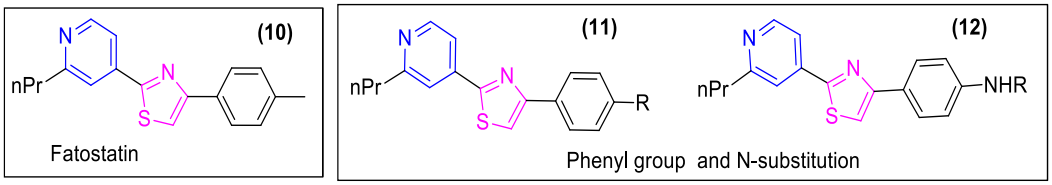


Aminothiazole scaffold from TAACF HTS Campaign

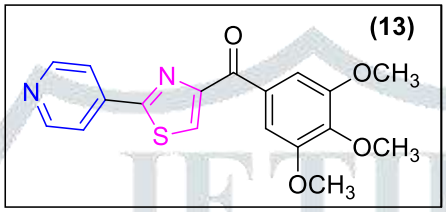
Samir Bondock et al [34] synthesized a series of novel 2-(3-pyridyl)-4,5-disubstituted thiazoles **(9)** and characterized by spectral and elemental analyses. The newly synthesized compounds were evaluated for their in vitro antimicrobial activity against ten bacterial and five fungal human pathogenic strains . From structure activity relationship (SAR) point of view, increasing the size of the substitutions either at position 4 or 5 on the thiazole nucleus decreased the antimicrobial activity.



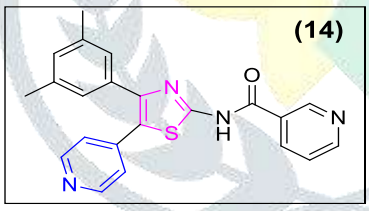
Fatostatin **(10)** is composed of three aromatic rings : pyridine, thiazole, and toluene. Fatostatin (125B11) was originally discovered from a chemical library as a synthetic small molecule that inhibited insulin-induced adipogenesis and serum-independent growth of cancer cells in cell culture.[35] Fatostatin inhibits activation of sterol regulatory element-binding protein (SREBP), blocks biosynthesis and accumulation of fat in obese mice. The methyl group of toluene is often oxidized in vivo by cytochrome P450. Therefore, the effects of substitutions of the toluene moiety of fatostatin were examined by Salih J. Wakil et al [36] and synthesized a series of fatostatin derivatives **(11 and 12)**, led to the identification of N-(4-(2- (2-propylpyridin-4-yl) thiazol-4-yl) phenyl) methanesulfonamide (FGH10019) as the most potent drug like molecule among the analogues tested with high aqueous solubility and membrane permeability and may serve as a seed molecule for further development.



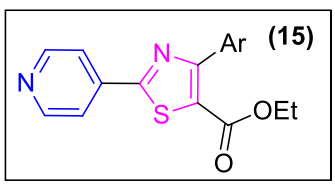
A series of 4-substituted methoxybenzoyl-aryl-thiazoles **(13)** (SMART) have been discovered and synthesized as a result of structural modifications of the lead compound 2-arylthiazolidine-4-carboxylic acid amides (ATCAA) by Yan Lu et al.[37] The antiproliferative activity of the SMART agents against melanoma and prostate cancer cells was improved from μM to low nM range compared with the ATCAA series. Preliminary mechanism of action studies indicated that these compounds exert their anticancer activity through inhibition of tubulin polymerization. Present SAR studies revealed that 3,4,5-trimethoxyphenyl was the essential group to keep excellent antitumor potency. *p*-Fluoro, *p*-NH2, and *p*-CH3 substituents in phenyl ring will increase the activity in place of 4-pyridyl ring , with no clear difference in effect on activity between EWG and EDG substituents The carbonyl linkage played an important role for the high potency.



Miwatashi et al. reported 4-phenyl-5-pyridyl-1,3-thiazole derivatives **(14)** as potent adenosine A_3R antagonists.[38] The compounds possessed nanomolar range activity with good selectivity over other adenosine receptor subtypes. Pharmacokinetic studies demonstrated good oral absorption profile and bioavilability. Molecular docking studies of this compound displayed good binding in active site of A_3R and necessary interactions with active amino acids.

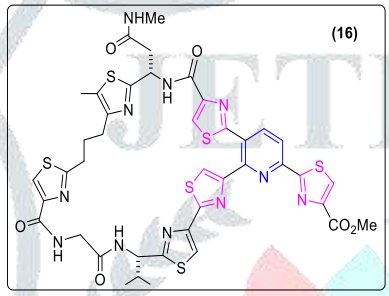


The Cell division cycle 7 (Cdc7) protein kinase is essential for DNA replication and maintenance of genome stability. Andreas Reichelt et al [39] systematically explored trisubstituted thiazole-based compounds **(15)** as inhibitors of Cdc7 kinase activity in cancer cells. Cdc7 has been considered as a novel target for cancer therapy.[40,41,42] The studies resulted in the identification of a potent, selective Cdc7 inhibitor that decreased phosphorylation of the direct substrate MCM2 in vitro and in vivo, and inhibited DNA synthesis and cell viability in vitro. Synthesis and SAR of trisubstituted thiazoles as a protein kinase inhibitors, for their low molecular weight and high binding efficiency is proved.

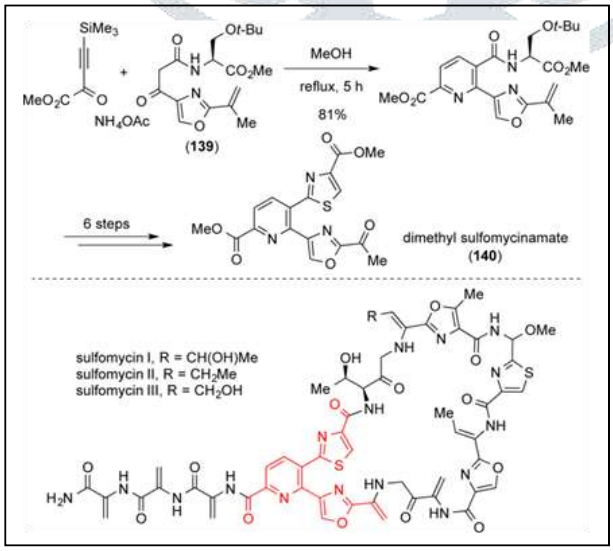


III. Pyridyl-thiazoles - as thiopeptide antibiotics

The increasing trend in the resistance to antibacterial agents has made it necessary to develop new chemical entities with low side effects and no resistance. A library of new thiazole derivatives have been reported and proved to be efficient as compared to β-lactam antibiotics regarding bacterial resistance. Thiopeptide antibiotics are a group of highly modified peptide metabolites**.** Hughes R. A. et al reported the total synthesis of the Thiopeptide Antibiotic Amythiamicin D **(16)** . Thiostrepton or thiopeptide are a class of sulfur containing highly modified cyclic peptides characterised by several common structural features that is the presence of thiazole and a centerpiece heterocycle containing tri or tetrasubstituted pyridine all in a macrocyclic array [43,44] possessing cytotoxic, antimicrobial and free radical scavenging activity. The thiopeptide antibiotics are a class of sulfur containing highly modified cyclic peptides with interesting biological properties, including reported activity against MRSA and malaria.

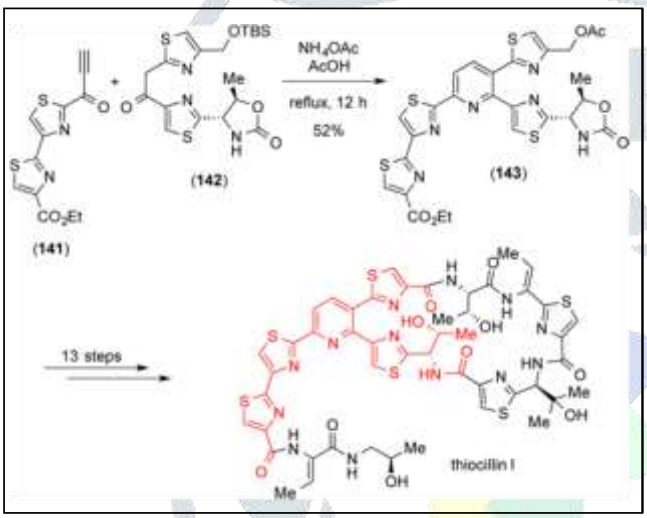


Sulfomycins are members of the thiopeptide group of antibiotics. Bagley and coworkers [45] synthesized a central oxazole-thiazole-pyridine domain of sulfomycins I−III . Use of a functionalized β-ketoamide led to dimethyl sulfomycinamate , (**Scheme 2**). The multicomponent Bohlmann−Rahtz reaction proceeded in 81% yield, and different steps were necessary to complete the synthesis of dimethyl sulfomycinamate.



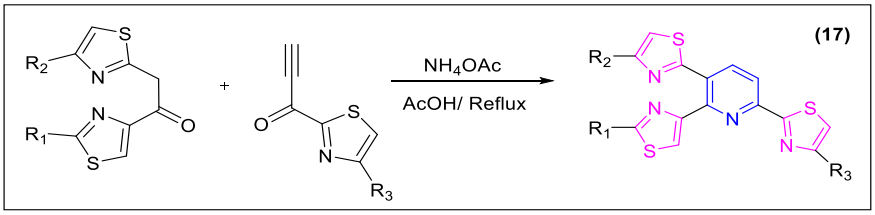
Scheme 2. Application of the Bohlmann−Rahtz Reaction to the Synthesis of Dimethyl Sulfomycinamate

Thiocillin I and its congeners are thiopeptide antibiotics [46] isolated from Bacillus cereus.[47] This substance has become of special significance in recent times, notably through the work of Walsh,[48] in that biosynthetic investigations have enabled the production of analogues displaying useful biological properties through the genetic manipulation of producing organisms. Such efforts could lead to novel anti-infective agents with improved therapeutic properties, thereby alleviating the ongoing antibiotic crisis.[49] Thiocillin I is another natural product from this family; its total synthesis was completed in 2011 by Aulakh and Ciufolini.[50] The pyridine-thiazole core was assembled by a three-component reaction involving substituted alkynone , 1,2-bisthiazolo-ethynone , and ammonium acetate in refluxing acetic acid **(Scheme 3).** Under these conditions the trisubstituted pyridine , in which the TBS protecting group was cleaved and replaced by an acetate group, was obtained in 52% yield. Completion of the synthesis of thiocillin I was achieved in 13 steps



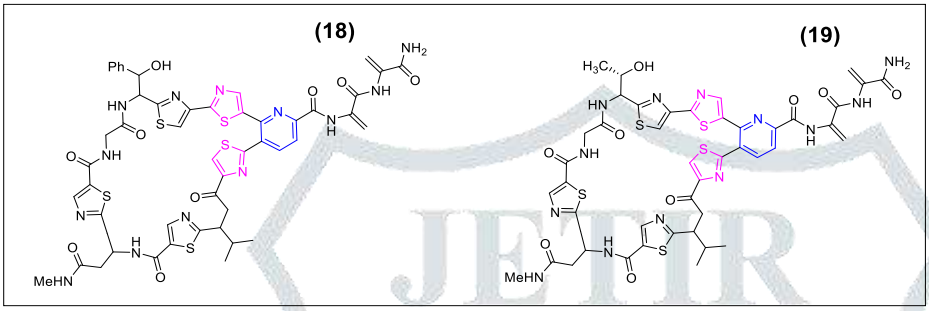
Scheme 3 : Total Synthesis and Complete Structural Assignment of Thiocillin I

Marco A. Ciufolini et al [51] have produced noteworthy methods for the assembly of the pyridine-thiazole core of thiopeptide antibiotics **(17)** . The biomedical potential of thiopeptide antibiotics [52] and the manifold chemical issues associated with a synthetic attack on these molecules have elicited considerable activity during the past decade.[53] The oxidation of 2-Methylthiazoles to 2-Formylthiazoles simplifies the implementation of the Bagley variant of the Bohlmann-Rahtz reaction as a key step **(Scheme 4)** in a concise new route to pyridine cores of thiopeptide antibiotics.

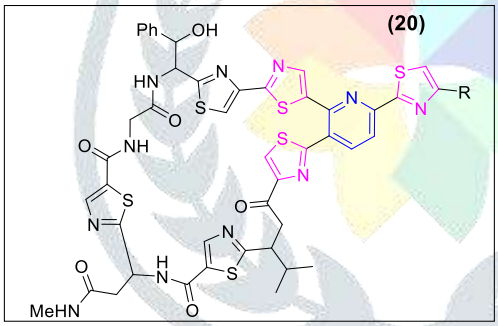


Scheme 4. One-Step Bohlmann-Rahtz Synthesis of Thiopeptide Cores

Bulbul P. *et al* [54] reported the proteasome inhibitory activity of compound (**18**) having central pyridine and substituted thiazole ring in its structure. Compound (**18**) is a naturally occurring thiopeptide antibiotic, characterized by highly complex sulfur-containing heterocyclic rings which has demonstrated a variety of physiological activities including antibacterial, antiparasitic. Thiazole peptide antibiotics block protein synthesis in bacteria targeting ribosome**.** Andrei L. G.[55] reported the synthesis of modified natural thiazole peptide antibiotic wherein the side chain phenyl was replaced by methyl group and demonstrated that the modified derivative (**19**) showed enhanced inhibitory activity (55 times more active than the natural antibiotic).



Wided H. *et al*.[56] synthesized 2-(hetero) arylated pyridines (Antibiotic GE 2270) **(20)** and showed to posses good anti-biotic and anti-inflammatory activities.

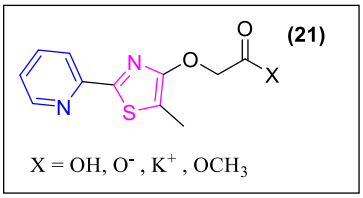


IV. Pyridyl-thiazoles - highly luminescent heterocyclic compounds

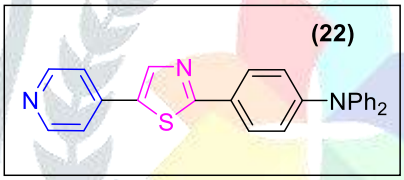
Five membered heterocycles containing two heteroatom's at 1,3 relative position possess certain level of flexibility compared with the condensed 1,3 Azoles. These compounds possess three carbon atoms to which a wide variety of substituents can be attached. Depending on the size of the introduced substituents the core structure may adopt twisted three dimensional structure. This feature may give rise to their unique fluorescent properties. Incorporation of electron-donating and attracting groups to an appropriate positions of monocyclic heteroaromatic compounds provides D-A molecules. [57] Increasing attention has been paid to fluorescent 1,3-Imidazoles, [58] oxazoles [59] and thiazoles. [60]

Ulrich-W. Grummt et al [61] reported an acid-base properties of 5-Methyl-2-Pyridine-2-yl-1,3-Thiazole-4-yl-oxyacetic acid (PTOA) and its methyl ester **(21)** as well as on the fluorescence properties of these molecules. PTOA is a highly fluorescent bidentate ligand. According to calculations, the alkoxy substituent

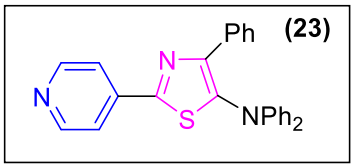
is essential for the longest wavelength transition. This group causes a considerable bathochromic shift with respect to the unsubstituted 2,2'-Pyridylthiazoles . Fluorescence quantum yields close to unity are found. Large Stokes shift values are explained by the shortening of the inter-ring bond in the excited state. These compounds may be useful for metal sensing and as laser dyes.



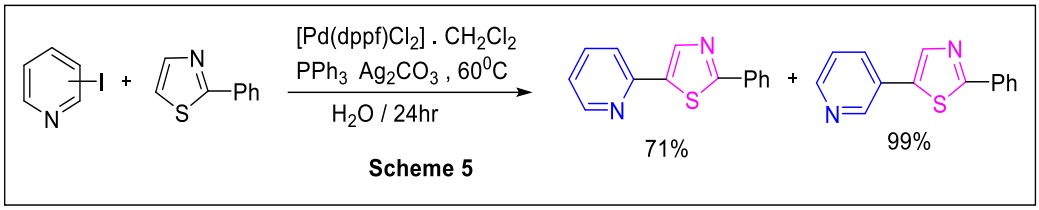
A family of linear asymmetrical D–π–A and symmetrical D–π–D types of thiazole-based aromatic heterocyclic fluorescent compounds **(22)** bearing various electron-donating and electron-withdrawing tails (bromo, triphenylamino, pyridyl, thienyl and benzoic acid) have been designed and prepared successfully by Wei Huang et al.[62] Synthetic, structural, thermal, spectral and computational comparisons have been carried out for related compounds because of their adjustable electronic properties. All of these multiple N-donor-containing compounds have effective π-conjugated systems and different triphenylamino, pyridine, thiophene, and benzoic acid tails showing symmetrical D–π–D and asymmetrical D–π–A structures.



Toshiaki Murai et al [63] reported synthesis of 1,3-Azoles using metal-free coupling reaction between secondary thioamides and thioformamides with diarylamino groups attached to the 5-position . This method is in marked contrast to the established method for preparing thiazoles using primary thioamides, which is known as Hantzsch thiazole synthesis. [64] The resulting 5-aminothiazoles **(23)** adopt highly deviated conformations, but they show strong blue fluorescence.

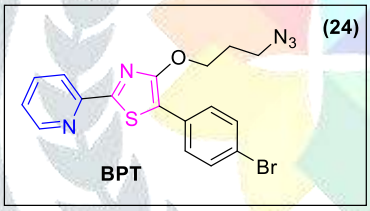


Greaney and co-workers [65] developed the first direct C_5-heteroarylation of 2-arylthiazoles with aryl iodides on water **(Scheme 5)**. The reactions were performed at 60^0c in the presence of Ag_2CO_3 and $[Pd(dppf)Cl_2]$ .CH_2Cl_2/PPh_3 catalyst.



Scheme 5

Fluorescent dyes are widely used for detection and monitoring in the fields of chemistry, biochemistry, molecular biology, medicine and material sciences. Due to sensitive and selective detection methods and unproblematic toxicology they have almost completely replaced radioactive tags. Widely used representatives include dansyl chloride, fluoresceins, rhodamines and boron-dipyrromethenes (BODIPYs). [66] Molecular probes are widely used tools in chemical biology that allow tracing of bioactive metabolites and selective labeling of proteins and other biomacromolecules. A successful class of fluorophores also used for probing in life science comprises the heterocyclic thiazoles. This structural element can be found in commercial products, such as thiazole orange, SYBR® Green I or TOTO®, which are, e.g., used for DNA labelling. In these compounds the thiazole ring is part of a benzothiazole. Based on the luminescent properties of pyridylthiazoles George Pohnert et al [67] reported the synthesis of BPT (4-(3-azidopropoxy)-5-(4-bromophenyl)-2-(pyridin-2-yl)thiazole) **(24)** with superior properties for fluorescence, UV and mass detection compared to other common reporters

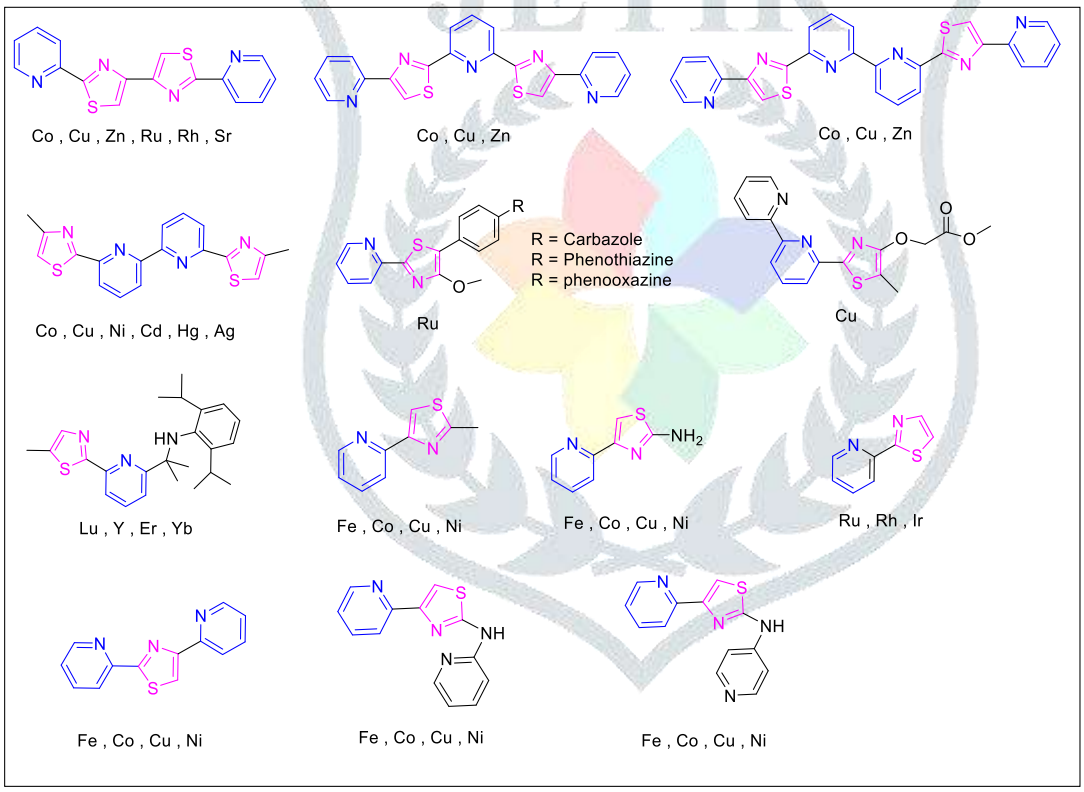


V. Pyridyl-thiazoles -as ligand in coordination chemistry

A vast number of 1,3-Thiazole-based compounds were described in the literature as ligands due to their capacity to coordinate different metal ions. [68] The coordinating ability of thiazolyl ligands is largely attributed to the presence of nitrogen and sulfur atoms in the five-membered ring as potential donor sites. Concerning the coordinating power of S and N atoms in 1,3-Thiazole ring, commonly, the nitrogen atom is much more effective as donor than sulfur. Furthermore, the nature of the metal as well as the substituents on the heterocyclic ligand are important in determining the exact nature of these ligand metal interactions. The 1,3-Thiazole fragment can connect several donor atom containing fragments of recognized coordination ability (e.g. pyridyls), thus creating bridging ligands and acting as a spacer. This type of functionality has been particularly applied in the syntheses of different coordination oligomers, polymers and metal coordination frameworks. The common structural base for all these compounds is a biheteroaryl pyridyl-thiazole.

As it can be seen from structures that, thiazoles possess a great potential for modification and introduction of a variety of substituents with electron donating heteroatoms. For instance, pyridyl-, carboxylic-,amido-,

phosphine- and many other groups possessing coordination ability can be placed in position 2 of the five-membered ring. Another notable application of 1,3-thiazole derivatives as ligands was described by Luconi and colleagues in 2014. [69] The authors designed several neutral bis(alkyl)-organolanthanidecomplexes of specifically tailored tridentate {N,N,N} 5-methylthiazole- or benzothiazole-amidopyridinate ligands, and showed that the nature of the thiazole unit (benzothiazole vs. 5-methylthiazole) controls the complex stability in solution. The complexes performed well as homogeneous catalysts in the industrially important isoprene polymerization, after activation with some organoborates. The activation with organoborates generates homogeneous catalytic systems for living isoprene polymerization with activity and selectivity depending on the nature of the metal ion and theused activator(s). In the Lu^{3+}complex, a rearrangement of ametal coordination sphere occurs through a metal-to-ligandalkyl migration with subsequent benzothiazole ring-opening andgeneration of the Lu^{3+}mono(alkyl)-arylthiolate species stabilized by a tetradentate {N,N,N,S} dianionic ligand. Depending on the rare-earth ion, a prevalent trans-1,4 or 3,4 regioselectivity in the polymer microstructure can be assessed very recently by Lyubov and co-workers.[70,71,72,73.]



Structures of Pyridyl-thiazole ligands in the preparation of metal complexes and the metal atoms

Conclusions

The biheteroaryl pyridyl-thiazole derivatives possess significant applications in diverse fields such as medicinal, agro-chemistry, light harvesting , cosmetic industry , catalysis, molecular switches, production of LEDs , photochromes , nonlinear optical materials and many more. In this review, we examined the potentialities of representative pyridylthiazoles, as ligands for the construction of various types of metal coordination compounds and metal–organic architectures with different complexities and uses. From the

literature survey it is clear that the applications of this biheteroaryl as catalysts, drugs and functional materials have a promising future.

By considering the importance and applications of this biheteroaryl (pyridyl-thiazole) in different areas like coordination complexes , medicinal , fluoroscence and there has always been a need for new and novel chemical entities with diverse biological activities. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesize pharmacologically interesting compounds. During the course of our research work, several entities containing pyridyl-thiazole have been designed, generated and characterized using spectral studies and are reported in relevant chapters.

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REFERENCES

1. Gusmeroli M. ; Ciapessoni A. ; Bettarini, F. ; Osti S. ; Mirenna L. ; Camaggi G. ; Gironda R. ; PCT Patent WO 2003050096. **2003**.
2. Kerdesky F. A. ; Holms J. H. ; Moore J. L. ; Bell R. L. ; Dyer R. D. ; Carter G. W. ; Brooks D. W. ; *J. Med. Chem* . **1991**, *34*, 2158.
3. (a) Dolling K. ; Zaschke H. ; Schubert H. ; *J. Prakt. Chem.* **1979** , 321, 643. (b) Kiryanov A. A. ; Sampson P. ; Seed A.J. ; *J. Org. Chem*. **2001** , 66 , 7925. (c) Mori A. ; Sekiguchi A. ; Masui K. ; Shimada T. ; Horie M. ; Osakada K. ; Kawamoto M. ; Ikeda T. ; *J. Am. Chem. Soc*. **2003**, 125, 1700.
4. Wu Y. ; Xie Y. ; Zhang Q. ; Tian H. ; Zhu W. ; Li A.D.Q. ; *Angew . Chem.* **2014** , 53, 2090.
5. Kim B.Y. ; Kim H.S. ; Helal A. ; *Sens. Actuators B : Chem*. **2015**, 206, 430.
6. Bach T. ; Heuser S. ; *Tetrahedron Lett.* **2000**, 41 1707.
7. Karamthulla S. ; Pal S. N. ; Md. Khan ; Choudhury L. H. ; *RSC Adv.* **2014** , 4, 37889.
8. Raper E. S. ; *Coord. Chem. Rev*. **1996**, 153, 199.
9. Raper E. S. ; *Coord. Chem. Rev*. **1997**, 165, 475.
10. Raper E. S. ; *Coord. Chem. Rev.* **1994**, 129 , 91.
11. Stangeland E. L. ; Tarek S. ; *J. Org. Chem.* **2004**, *69*, 2381-2385.
12. Yoshimura S. ; Tsuruni T. ; Takase, S. ; Okuhara M. ; J. *Antibiotics.* **1995**, *48*, 1073.
13. Tsuruni Y. ; Ueda H. ; Hayashi K. ; Takase S. ; Nishikawa M. ; Kiyoto S. ; Okuhara M. ; *J. Antibiotics.* **1995**, *48*, 1066.
14. (a) Patt W. C. ; Massa M. A. ; *Tetrahedron Lett.* **1997**, *38*, 1297.
(b) Massa M. A. ; Patt W. C. ; Ahn K. ; Sisneros A. M. ; Herman S.B. ; Doherty A. ; *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2117.
15. Huang S. T. ; Gordon D. M. ; *Tetrahedron Lett.* **1998**, *39*, 9335.
16. Bach T. ; Heuser S. ; *Syn. lett.* **2002**, 20, 89.
17. Pola S.; doi.org/10.5772/62077.
18. Van Muijlwijk-Koezen J. E ; Timmerman H. ; Vollinga R. C. ; Frijtag von Drabbe Kunzel J. ; DeGroote M. ; Visser S. ; IJzerman A. P. ; *J. Med. Chem.* **2001** , 749-762. doi :10.1021/jm0003945.
19. Makam P. ; Kannan T.; *Eur. J. Org. Chem.* **2014**, 09, 086. doi : 10.1016/j.ejmech.

20. Lu Y. ; *J. Med. Chem.* **2011,** 54, 4678–4693. doi: 10.1021/jm2003427.
21. Lu Y. ; *J. Med. Chem.* **2009** , 52, 1701–1711, doi: 10.1021/jm801449a.
22. Zheng S. *; J Med Chem.* **2014** , 57**,** 6653–6667, doi: 10.1021/jm500724x
23. Zhou W. ; *Eur. J. Org. Chem*. **2015**, 96, 269–280. doi: 10.1016/j.ejmech.2015.04.027
24. Hay M. P. ; *J. Med. Chem.* **2010**, 53**,** 787–797, doi: 10.1021/jm901457w.
25. Kamisuki S. ; *J. Med. Chem.* **2011**, 54 **,** 4923–4927. doi: 10.1021/jm200304y .
26. Zhou W. ; Tang S. ; Sun Z. ; Yunqi Li . ; Dong Y. ; Haixiang P. ; Yangrui P. ; Jinhua W. ; Ting S. ; Jiang Z. ; Zhengfang Yi ; Yihua ; *Scientific Reports.* 6:33434 doi : 10.1038/srep33434 .
27. Dae-Kee K. ; Joon H. C. ; Young J. A. ; *Bioorg. Med. Chem. Lett.* **2008**. 2122 - 2127. doi : 10.1016/j.bmcl.2008.01.084
28. Meissner A. ; Helena I. ; Boshoff ; Mahalakshmi V. ; Benjamin P. ; Duckworth ; Clifton E. ; Barry ; Courtney C. Aldricha ; *Bioorg. Med. Chemistry*. **2013**, doi:http://dx.doi.org/10.1016/j.bmc.2013.08.048
29. Ananthan S. ; Faaleolea E. R . ; Goldman R. C. ; Hobrath J. V. ; Kwong C. D. ; Laughon B. E. ; Maddry J. A. ; Mehta A. ; Rasmussen L.; Reynolds R. C. ; Secrist J. A. ; Shindo N. ; Showe D. N. ; Sosa M. I. ; Suling W. J. ; White E. L. ; *Tuberculosis.* **2009,** *89*, 334.
30. Maddry J. A. ; Ananthan S. ; Goldman R. C. ; Hobrath J. V. ; Kwong C. D. ; Maddox C. ; Rasmussen L. ; Reynolds R. C. ; Secrist J. A. ; Sosa M. I. ; White E. L. ; Zhang, W. ; *Tuberculosis.* **2009,** *89*, 354.
31. Reynolds R. C. ; Ananthan S. ; Faaleolea E. ; Hobrath J. V. ; Kwong C. D. ; Maddox C. ; Rasmussen L. ; Sosa M. I. ; Thammasuvimol E. ; White E. L. ; Zhang W. ; Secrist J. A. ; *Tuberculosis.* **2012** , *92*, 72.
32. Brogden R. N. ; Heel R. C. ; *Drugs.* **1986,** *31*, 96.
33. Noble S. ; Balfour J. A. ; *Drugs.* **1996** , *51*, 424.
34. Bondock S. ; Naser T. ; Yousry A. ; *Eur. J. Org. Chem*. **2013**, 62 , 270-279
35. Choi Y.; Kawazoe Y. ; Murakami K.; Misawa, H. ; Uesugi, M.; *J. Biol. Chem*. 2003, 278, 7320–7324.
36. Kamisuki S. ; Shirakawa T. ; Kugimiya A. ; Lutfi Abu-Elheiga ; Young H. ; Park C. ; Yamada K. ; Shimogawa H.; Salih J.; Wakil ; Motonari U.; *J. Med. Chem.* **2011**, 54, 4923–4927. dx.doi.org/10.1021/jm200304y
37. Lu Y. ; Chien-Ming Li. ; Wang Z.; Ross C. R. ; Chen J. ; Dalton J. T. ; Wei Li ; Miller D. D. ; *J. Med. Chem.* **2009**, *52*, 1701–1711.
38. (a) Heller M. ; Schubert U. S. ; *Eur. J. Org. Chem*. **2003**, 947. (b) Henry G. D. ; *Tetrahedron* . 2004, 60, 6043. (c) Shestopalov A.; Shestopalov A.; Rodinovskaya L. ; *Synthesis.* **2008**, 1. (d) Hill, M. D. *Eur. J. Chem* **2010**, 16, 12052. (e) Bull J. A. ; Mousseau J. J. ; Pelletier G. ; Charette A. B. ; *Chem. Rev*. **2012**, 112, 2642. (f) Diaconescu, P. L. ; *Acc. Chem. Res*. **2010**, 43,1352. (g) Mousseau J. J. ; Charette A. B. ; *Acc. Chem. Res*. **2013**, 46, 412.(h) Rossi R. ; Bellina F.; Lessi M. ; Manzini C. *Adv. Synth. Catal*. **2014** ,356 , 17.
39. Reichelt A. ; *Eur. J. Org. Chem*., **2014**, 80, 364 -382
40. Ito S.; Taniyami C. ; Arai N.; Masai H.; *News & Perspectives*. **2008,** 21 , 481-488.
41. Montagnoli A. ; Moll J. ; Colotta F. ; *Clinical Cancer Research* , **2010**, 16, 4503-4508.
42. Swords R. ; Mahalingam D. ; Dwyer M. O. Santocanale C.; Kelly K.; Carew J.; Giles F.; *European Journal of Cancer* , **2010**, 46 , 33-40.
43. Zhu J. ; Bienayme H. ; *Multicomponent Reactions*; Germany , **2005**.
44. (a) Seiple I. B.; Su S. ; Rodriguez R. A. ; Gianatassio R. ; Fujiwara Y. ; Sobel A. L. ; Baran P. S. ; *J. Am. Chem. Soc.* **2010**, 132, 13194. (b) Li M.; Hua R.; *Tetrahedron Lett*. **2009**, 50, 1478. (c) Kobayashi O. ; Uraguchi D. ; Yamakawa T. ; *Org. Lett*. **2009**, 11, 2679. (d) Yanagisawa S.; Ueda K.; Taniguchi T. ; Itami

K. ; *Org. Lett.* **2008**, 10, 4673. (e) Mukhopadhyay S.; Rothenberg G.; Gitis D.; Baidossi M. ; Ponde D. E. ; Sasson Y. ; *J. Chem. Soc.*, Perkin Trans. 2 , **2000**, 1809.

45. Bagley M. C. ; Chapaneri K. ; Dale J. W. ; Xiong X. ; Bower J. ; *J. Org. Chem.* **2005**, 70, 1389.

46. (a) Bagley M. C.; Dale, J. W.; Merritt E. A. ; Xiong X. ; *Chem. Rev.* **2005**, 105, 685. (b) Hughes R. A. ; Moody C.; *J. Angew. Chem.*, Int. Ed. 2007, 46, 7930. (c) Arndt H. D. ; Schoof S. ; Lu J.Y. ; *Angew. Chem.*, Int. Ed. **2009**, 48, 6770.

47. (a) Shoji J. ; Hinoo H.; Wakisaka Y. ; Koizumi K. ; Mayama M. ; Matsuura, S. ; Matsumoto K. ; *J. Antibiot.* **1976**, 24, 366. (b) Shoji J. ; Kato T. ; Yoshimura Y. ; Tori K. ; *J. Antibiot.* **1981**, 29, 1126.

48. (a) Acker M. G.; Bowers A. A. ; Walsh C. J.; *J. Am. Chem. Soc.* **2009**, 131, 17563. (b) Bowers A. A.; Walsh C. J. ; Acker M. G.; *J. Am. Chem. Soc*. **2010**, 132, 12182. (c) Bowers A. A.; Acker M. G. ; Koglin A. ; Walsh C. J. ; *J. Am. Chem. Soc.* **2010**, 132, 7519. (d) Walsh C. J. ; Acker M. G. ; Bowers A. A. ; *J. Biol. Chem.* **2010**, 286, 27525.

49. (a) Wieland Brown L. C.; Acker M. G.; Clardy J.; Walsh C. T. ; Fischbach M. A.; *Proc. Natl. Acad. Sci.* U.S.A. **2009**, 106, 2559. (b) Liao R.; Duan L.; Lei C.; Pan H.; Ding Y.; Zhang Q.; Chen D.; Shen B.; Yu Y. ; *Chem. Biol*. **2009**, 16, 141.

50. (a) Aulakh V. S. ; Ciufolini M. A. ; *J. Org. Chem*. **2009**, 74, 5750.
(b) Aulakh,V. S. ; Ciufolini M. A. ; *J. Am. Chem. Soc*. **2011**, 133, 5900.

51. Aulakh V. S. ; Ciufolini M. A. ; *J. Org. Chem.* **2009 ,** 74, 5753

52. (a) Bagley M. C. ; Dale J. W. ; Merritt E. A. ; Xiong X. ; *Chem. Rev*. **2005**, 105, 685.
(b) Hughes R. A. ; Moody C. ; *J. Angew. Chem*. **2007**, 46, 7930.

53. (a) Moody C. J. ; Bagley M. C. ; *Chem. Commun.* **1998**, 2049. (b) Bagley M. C. ; Bashford K. E. ; Hesketh C. L. ; Moody C. J. ; *J. Am. Chem. Soc*. **2000**, 122, 3301. (c) Hughes R. A.; Thompson S. P. ; Alcaraz L. ; Moody C. J.; *J. Am. Chem. Soc.* **2005**, 127, 15644. (d) Hughes R. A. ; Thompson S. P. ; Alcaraz L. ; Moody C. ; *J. Chem. Commun*. **2004**, 946. (e) Nicolaou K. C.; Safina B. S. ; Zak M. ; Lee S. H.; Nevalainen M . ; Bella M. ; Estrada A. A.; Funke C. ; Zecri F. J. ; Bulat S. ; *J. Am. Chem. Soc*. **2005**, 127, 11159. (f) Nicolaou K. C. ; Zak M. ; Safina B. S. ; Estrada A. A.; Lee S. H. ; Nevalainen M. ; *J. Am. Chem. Soc.* **2005**, 127, 11176. (g) Nicolaou K. C.; Safina B. S.; Zak M. ; Estrada A. A. ; Lee S. H. *Angew. Chem.*, Int. Ed. **2004**, 43, 5087. (h) Nicolaou K. C. ; Zak M. ; Safina B. S. ; Lee S. H. ; Estrada A. A. ; Siomycin A. ; *Angew. Chem*. **2004**, 43, 5092. (i) Mori T.; Higashibayashi S. ; GotoT.; Kohno, M.; Satouchi, Y.; Shinko, K.; Suzuki, K.; Suzuki S.; Tohmiya H. ; Hashimoto K. ; Nakata M. *Tetrahedron Lett*. **2007**, 48, 1331. (j) Nicolaou K. C. ; Zou B. ; Dethe D. H. ; Li D. B. ; Chen D. Y. K. ; *Angew. Chem.* **2006**, 45, 7786. (k) Muller H. M. ; Delgado O. ; Bach T. ; *Angew. Chem*. **2007**, 46, 4771. (l) Delgado O. ; Muller H. M. ; Bach T. *Chem. Eur. J*. **2008**, 14, 2322. (m) Lefranc D. ; Ciufolini M. A. *Angew. Chem*. **2009**, 48, 4198.

54. Bulbul P. ; Bhat U.; *Cancer Biology & Therapy*. **2011**, *11*, 43.

55. Andrei L. G. ; *Cancer Biology & Therapy*. **2011**, *11*, 56.

56. Wided H. ; Neji B. ; Srasra ; Henri D ; Jean-Francois S. ; ***RSC Adv.* 2016**, ***6,*** 17110.

57. (a) Schwartz P. O. ; Biniek L.; Zaborova E.; Heinrich B.; Brinkmann M.; Leclerc N. ; Méry S. ; *J. Am. Chem. Soc.* **2014**, 136, 5981. (b) Li T.; Gao J.; Cui Y. ; Zhong C. ; Ye Q. ; Han L. ; *J. Photochem. Photobiol-A.* **2015**, 303-304, 91. (c) Nakagawa T.; Yamaji M. ; Maki S.; Niwa H.; Hirano T.; *Photoche. Photobiol.* **2015**, 91,807.

58. (a) Martorana A.; Pace A.; Buscemi S.; Piccionello A. P., *Org. Lett.* **2012**, 14, 3240. (b) Chen C. Y. ; Hu W. P. ; Yan P. C. ; Senadi G.C. ; Wang J. ; *Org. Lett.* **2013**, 15, 6116. (c) Leit M. J. ; Krylova V. A. ; Djurovich P. I.;

Thompson M. E. ; Yersin H. ; *J. Am. Chem. Soc.* **2014**,136, 16032. (d) Mutoh K.; Nakagawa Y. ; Sakamoto A. ; Kobayashi Y.; Abe J.; *J. Am. Chem. Soc.* **2015**, 137, 5674. (e) Yamashita H. ; Ikezawa T.; Kobayashi Y. ; Abe J., *J. Am. Chem. Soc*. **2015**, 137, 4952.

59. (a) Charier S. ; Ruel O.; Baudin J. B.; Alcor D.; Allemand J. F.; Meglio A.; Jullien L.; *Angew. Chem.*, **2004**, 43, 4785. (b) Iliashenko R. Y.; Zozulia O. S.;Cent. Doroshenko A. O. ; *Eur. J. Chem.* **2011**, 9, 962. (c) Iliashenko R. Y. ; Gorobets N. Y. ; Doroshenko A. O. ; *Tetrahedron Lett.* **2011**, 52, 5086. (d) Mahuteau- Betzer F.; Piguel S.; *Tetrahedron Lett.* **2013**, 54, 3188. (e) Kwon J.E. ; Park S. ; *J. Am. Chem. Soc*. **2013**, 135, 11239. (f) Borodin O.O. ; R.Il'yashenko Yu A. O. ; Doroshenko ; *Chem. Heterocycl. Compd.* **2014**, 50, 379.

60. (a) Helal A. ; Kim H. G.; Ghosh M. K. ; Choi C. H.; Kim S.H. ; Kim H. S. ; *Tetrahedron.* **2013**, 69, 9600. (b) Nagura K. ; Saito S. ; Yusa, H. ; Yamawaki, H. ; Fujihisa H. ; Sato Y. ; Shimoikeda S. ; Yamaguchi ; *J. Am. Chem. Soc.* **2013**, 135, 10322. (c) Mishra B. ; Shekar K. P. C. ; Kumar A.; Phukan S. ; Mitra S. ; Kumar D. ; *J. Heterocyclic Chem.* **2013**, 50, 125. (d) Zheng M. H. ; Sun W. ; Jin J.Y. ; Yan C. H. ; *J. Fluoresc.* **2014**, 24, 1169. (e) Wolfram S. ; Würfel H. ; Habenicht S. H. ; Lembke C. ; Richter P. ; Birckner E. ; Beckert R. ; Pohnert G. ; *Beilstein J. Org. Chem.* **2014**, 10, 2470. (f) Gautam D. ; Chaudhary R. P. ; *Spectrochim. Acta, Part A*, **2015**, 143, 256. (g) Zhang X. ; Jing S. Y. ; Huang S. Y. ; Zhou X. W. ; Bai J. M. ; Zhao B. X. ; *Sens. Actuators, B* , **2015**, 206, 663. (h) Tanaka S. ; Ashida K. ; Tatsuta G. ; Mori A. ; *Synlett* , **2015**, 26, 1496.

61. Ulrich W. ; Grummt Dieter Weiss ; Birckner E.; Beckert R. ; *J. Phys. Chem. A* **2007,** *111*, 1104-1110

62. Tao T. ; Bin-Bin M. ; Yu-Xin P. ; Xiao-Xu Wang, Wei Huang,* and Xiao- Zeng You dx.doi.org/10.1021/jo401384g | *J. Org. Chem.* **2013**, 78, 8669−8679

63. Yamaguchi K., Murai T., Hasegawa S., Miwa Y., Kutsumizu S., Maruyama T., Sasamori T. and Tokitoh N.. *J. Org. Chem.* (2015), 80, 10742−10756

64. Kempson J. ; In Name Reactions in Heterocyclic Chemistry II; J. J. Li, Ed.; Jon Wiley & Sons: New York, **2011** , 299.

65. Turner G. L. ; Morris J. A. ; Greaney M. F. ; *Angew. Chem.* **2007**, 119, 8142. 66. Sadaghiani A. M. ; Verhelst S. H. L. ; Bogyo M. ; *Curr. Opin. Chem. Biol.* **2007,** *11*, 20–28.

67. Wolfram S. ; Würfel H. ; Habenicht S. ; Lembke C. ; Richter P. ; Birckner E.; Beckert R. ; Pohnert G. ; *Beilstein J. Org. Chem.* **2014**, *10*, 2470–2479.

68. Luis M.T. ; Armando F. ; Pombeiro J. L. ; Maximilian N. ; Kopylovich Centro de ; Química E. ; Complexo I . ; *Portugal Coordination Chemistry Reviews* . **2016**, 308 , 32–55.

69. Luconi L. ; Lyubov D.M. ; Rossin A. ; Glukhova T.A. ; Cherkasov A.V. ; Tuci G. ; Fukin G.K. ; Trifonov A.A. ; Giambastiani G. ; *Organometallics* . **2014**, 33 ,7125.

70. Gras M. ; Therrien B. ; Süss-Fink G. ; Casini A. ; Edafe F. ; Dyson P. J., *J. Organomet. Chem*. 695 , **2010** , 1119.

71. Menzel R .; Kupfer S.; Mede R.; Wei D.; Görls H.; González L.; Beckert R.; *Eur. J. Org. Chem.* **2012**, 5231.

72. Menzel R.; Wei D. ; Täuscher E.; Beckert R.; Görls H.; *Inorg. Chem. Commun*.18 , **2012**, 65.

73. Huxel T.; Leone S.; Lan Y.; Demeshko S.; Klingele J.; *Eur. J. Inorg. Chem.* **2014**, 3114.