CHAPTER-1

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1.1 Review on Triazine derivatives

The triazine structure is a heterocyclic ring, analogous to the six-membered benzene ring but with three carbons replaced by nitrogens. The three isomers of triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine. Other aromatic nitrogen heterocycles are pyridines with 1 ring nitrogen atom, diazines with 2 nitrogen atoms in the ring and tetrazines with 4 ring nitrogen atoms. Triazines are weaker bases than pyridine.

\[ \text{1,2,3-triazine} \quad \text{1,2,4-triazine} \quad \text{1,3,5-triazine} \]

The best known 1,3,5-triazine derivative is melamine with three amino substituents used in the manufacture of resins. Another triazine extensively used in resins is benzoguanamine. Triazine compounds are often used as the basis for various herbicides such as cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). Chlorine-substituted triazines are also used as reactive dyes. These compounds react through a chlorine group with hydroxyl groups present in cellulose fibres in nucleophilic substitution, the other triazine positions contain chromophores. Mixtures of Triazines and water are also used to remove H\(_2\)S from natural gas.

A series of 1,2,4-triazine derivatives known as BTPs have been considered in the liquid-liquid extraction community as possible extractants for use in the advanced nuclear reprocessing of used fuel. BTPs are molecules containing a pyridine ring bonded to two 1,2,4-triazin-3-yl groups. Triazine-based molecules have been used as bridging ligands to bind three dinuclear arene ruthenium (or osmium) compounds to
form metallaprisms. S-Triazine derivatives represent an important class of compounds due to their potential to be biologically active. They are known to be anti-protozoals, \cite{1}, anticancer agents, estrogen receptor modulators, antimalarials, cyclindependent kinase modulators, \cite{2} and antimicrobials. Cyanuric chloride, an inexpensive, easily available reagent, of low toxicity and less corrosive than other similar reactants, has been widely used in organic reactions. 1,3,5-triazines (or s-triazines) are a class of compounds well known for a long time and still continue the object of considerable interest mainly due to their application in different fields, including the production of herbicides and polymer photostabilizers. Some 1,3,5-triazines display important biological properties; for example hexamethylmelamine (HMM) & 2-amino-4-morpholino-s-triazine are used clinically due to their antitumor properties to treat lung, breast and ovarian cancer, respectively. \cite{3} The diverse biological activities observed for different molecule containing the 1,3,5-triazine unit have been further explored in order to discover other new potential molecules through the synthesis of libraries by combinatorial approaches. Certain 1,3,5-triazine derivatives are also used as chiral stationary phases, for example, the chiral solvating agent for the determination of enantiomeric excess by NMR spectroscopy and determination of absolute configuration by circular dichroism.

Thus owing to the above stated importance of this ligand having s-triazine and 8-hydroxyquinoline (8-HQ) and their systematic literature survey we were interested to synthesize coordination polymers based on ligands prepared from s-triazine-ether, 5-amino 8-Hydroxyquinoline and various phenol.

I.B.Johns and H. R. Dipietro \cite{4} reported structure of trimer of salicylonitrile, 2,4,6-tris(2-hydroxy phenyl)-s-triazine suggest that it should be coordinate with divalent tetracoordinate metal ion to form polymeric products.
Patrick Gamez, Paul de Hoog and Olivier Roubeau \cite{5} work on Copper(II) nitrate reacts with the rigid polydentate triple-connecting 2,4,6-(di-pyridin-2-yl-amino)-[1,3,5]triazine (dpyatriz) ligand in acetonitrile to an unprecedented infinite molecular ladder in which five-coordinated copper pseudo-dimers are bridged by nitrate anions and the coordination polymer chains are linked by hexacoordinated copper ions leading to the formation of large guest cavities.

Megumu Munakata and Ming Wen and Yusaku Suenaga \cite{6} work on carbon and nitrogen coordinated silver (I) polymers of 2,4,6-triphenoxy-1,3,5-triazine. For the purpose of furthering the understanding of steric structure effects upon coordination behavior and exploring the possibility of non-planar complexation in the triazine system for formation of extended polymeric structures, 2,4,6-triphenoxy-1,3,5-triazine(tpotz) has been reacted with silver(I) perchlorate and trifluoromethanesulfonate. The crystal structures of [Ag2(tpotz)3(ClO4)2] and...
\[\text{Ag}_2(\text{tpotz})_2(\text{CF}_3\text{SO}_3)_2(\text{THF})\] have been determined by single-crystal X-ray diffraction. Tpotz is rich in organic components that can offer potential sites for complexation, which can be utilized to generate an interesting array of organometallic compounds with one-dimensional chains.

Patrick Gamez, Paul de Hoog and Martin Lutz\textsuperscript{[7]} studied on coordination compounds from 1,3,5-triazine derived multi-directional ligands which useful for oxidation catalysis. A series of 1,3,5-triazine- and 2,2-dipyridylamine-based ligands have been prepared and the crystal structure from one of them was solved. The coordination of these dendritic multi-directional ligands with various metal salts led to attractive supramolecular architectures.
Differential reactivity of 1,3,5-triazines

Ligands prepared and tested in catechol oxidase activity
Yongquin wei, kechen wu and Ria broer [8] work on a polymeric cobalt compound \([\text{Co(DCNT)}(\text{H}_2\text{O})]_n\) with novel topology: Synthesis, structure, luminescence, and magnetic property. The hydrothermal reaction of \(\text{Co(NO}_3)_2\cdot 6\text{H}_2\text{O}\) and a new designed ligand \(\text{H}_2\text{DCNT}\) yields a three-dimensional polymer \([\text{Co(DCNT)}(\text{H}_2\text{O})]_n\) (1), \(\text{H}_2\text{DCNT}=2,4\text{-bis}(4\text{-carboxyphenylamino})-6\text{-diethylamino}-1,3,5\text{-triazine}\). In the structure \([\text{Co(DCNT)}(\text{H}_2\text{O})]_n\) each \(\text{DCNT}^2-\) has three coordination sites, one nitrogen atom in the triazine ring coordinating to \(\text{Co(II)}\) and two carboxylates adopting bridging mode, which make the infinite \(\text{Co(II)}\) chains array uniformly and evenly toward crystallographic c-axis. Luminescent and magnetic properties of \([\text{Co(DCNT)}(\text{H}_2\text{O})]_n\) were also studied.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{N} & \quad \text{Cl} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{H}_2\text{C}_2\text{H}_5 & \quad \text{N} & \quad \text{H}_2\text{C}_2\text{H}_5 \\
\text{Cl} & \quad \text{C}_2\text{H}_5 & \quad \text{Cl} & \quad \text{C}_2\text{H}_5 \\
\text{N} & \quad \text{C}_2\text{H}_5 & \quad \text{N} & \quad \text{C}_2\text{H}_5 \\
\text{H} & \quad \text{N} & \quad \text{H} & \quad \text{N}
\end{align*}
\]

**The structure and synthetic route of H\(_2\)DCNT**

Jignesh P. Raval, Amrita R. Rai and Nilesh H. Patel\textsuperscript{10} reported synthesis and invivo antimicrobial activity of N'-[4(arylamino)-6-(pyridin-2-ylamino)1,3,5-triazin-2-yl]benzohydrazide. Here, variety of N'-(4-(arylamino)-6-(pyrazin-2-ylamino)-1,3,5-triazin-2-yl)isonicotinohydrazide, were synthesized by using 2-aminopyridine, isonicotinic acid hydrazide and cyanuric chloride. And the structures of these compounds were confirmed by IR, NMR (\textsuperscript{1}H & \textsuperscript{13}C) spectral analysis. The newly synthesized compounds were also evaluated for antimicrobial activity against variety of bacterial strains and some of these compounds have shown significant antibacterial and antifungal activities.

![Chemical structure image]

Sonika Jain, Anamika Sharma, Meenakshi Agrawal\textsuperscript{11} reported synthesis and antimicrobial evaluation of some novel trisubstituted s-triazine derivatives based on isatinimino, sulphonamido and Azacarbazole.

![Chemical structure image]
K. N. Sarmah, N. K. Sarmah and Talha V. Patel \cite{12} studied synthesis, characterization and antimicrobial studies of certain triazole containing s-triazine derived compounds.

G. R. Jani, K. B. Vyas and Zudas Franco \cite{13} reported preparation and antimicrobial activity of s-triazine hydrazones of 7-hydroxy coumarin.

K. N. Sarmah, N. K. Sarmah and K. B. Kurmi \cite{14} reported synthesis of novel s-triazine derivatives as potential antibacterial agents.
Compounds | R1 | R2 | R3 |
--- | --- | --- | --- |
1a | Dicyclohexylamine | N-methyl piperazine | -Cl |
1b | Dicyclohexylamine | Monoethanolamine | -Cl |
2a | Benzimidazole | 2-chlorophenylthiourea | 2-chloro aniline |
2b | Benzimidazole | 4-chlorophenylthiourea | 4-chloro aniline |
2c | Benzimidazole | 4-chlorophenylthiourea | 4-fluoro aniline |
2d | Benzimidazole | 3-methylphenylthiourea | 3-methyl aniline |

Firdous D. Khan, Manjusha V. Yadav and Ashok D. Sagar [16] reported synthesis, characterization and antimicrobial evaluation of core s-triazine moiety.

Viktor Milata, Ladislav Reinprecht and Juraj Kizlink\textsuperscript{[18]} reported synthesis and antifungal efficacy of 1,3,5-triazines.

Anjani solankee, Kishor kapadia, Ana ciric, Marina sokovic and irini doytchinove\textsuperscript{[19]} reported synthesis of some new s-triazine based chalcones and their derivatives as potent antimicrobial drugs.

Carlos A. M. Afonso and co-workers [21] reported synthesis of 2,4,6-tri-substituted -1,3,5-triazines.

Nidhi Gautam and O P Chaourasia [22] reported synthesis, characterization and insecticidal activity of some new s-triazine derivatives of pyrazoline, pyrimidine, isooxazoline and isothiazoline moiety

Loredana Donati and Enzo Funari [24] reported review on leaching characteristics of triazines and their degradation products.

Kokila N. Sarmah and Talha V. Patel [25] reported synthesis, characteristics and antimicrobial studies of certain s-triazine derived compounds and analogs.

Akshay D. Desai, Dharmesh H. Mahajan and Kishor H. Chikhalia \textsuperscript{[27]} reported synthesis of novel aliphatic thiourea derivatives containing s-triazine moiety as potential antimicrobial agents.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{S} \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{NH} \quad \text{N} \quad \text{NH} \\
& \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{NH}
\end{align*}
\]

K. N. Sarmah, N. K. Sarmah and K. B. Kurmi \textsuperscript{[28]} studied synthesis and studies of biological evaluation of certain s-triazine derived compounds.

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{N} \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{NH} \quad \text{N} \quad \text{NH} \\
& \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{NH}
\end{align*}
\]

Sweta D. Desai and Arvind G. Mehta \textsuperscript{[29]} reported design, synthesis and biological evaluation of various N-substituted piperazine annulated s-triazine derivatives.
S. G. Kansara, R. D. Pandit and V. G. Bhawe\textsuperscript{[30]} reported synthesis of some new ibuprofen derivatives containing heterocyclic moiety like s-triazine and evaluated for their analgesic activity.

Vineeta sareen, vineeta khatri and Prakash jain\textsuperscript{[31]} reported synthesis of 2-(6-fluorobenzothiazole-2'-yl amino)-4-(phenylthioureido)-6-(substituted thioureido)-1,3,5-triazine as antimicrobial agent.
N. Sekar, Vikas S. Padalkar and Kiran R Phatangare\textsuperscript{[32]} reported synthesis and biological evaluation of novel 6-aryl-2,4-di substituted Schiff bases 1,3,5-triazine derivatives as antimicrobial agents.

Vikas S. Padalkar and Vikas S. Patil\textsuperscript{[33]} reported synthesis and photo physical properties of fluorescent 1,3,5-triazine styryl derivatives. It was found that the strong electron acceptor-donor chromophoric system of these compounds showed high Stoke's shift and excellent thermal stability. Compounds showed positive solvatofluorism behaviour from nonpolar to polar solvent. All compounds have good thermal stability.
Divya Karunakaram, Govindarajan R. and Srikanth Jupudi [34] reported synthesis and biological evaluation of newer s-triazine derivatives.
1.2 Brief details on Morpholine containing compounds and its biological activity

Morpholine \[^{[35]}\] is an organic chemical compound having the chemical formula O(CH\(_2\)CH\(_2\))\(_2\)NH. This heterocycle features both amine and ether functional groups. Because of the amine, morpholine is a base; its conjugate acid is called morpholinium. For example, treating morpholine with hydrochloric acid makes the salt morpholinium chloride.

\[
\begin{align*}
\text{N} & & \text{O} \\
\text{H} & & \text{O}
\end{align*}
\]

Morpholine is a common additive, in parts per million concentrations, for pH adjustment in both fossil fuel and nuclear power plant steam systems. Morpholine is used because its volatility is about the same as water, so once it is added to the water, its concentration becomes distributed rather evenly in both the water and steam phases. Its pH adjusting qualities then become distributed throughout the steam plant to provide corrosion protection. Morpholine is often used in conjunction with low concentrations of hydrazine or ammonia to provide comprehensive all-volatile treatment chemistry for corrosion protection for the steam systems of such plants. Morpholine decomposes reasonably slowly in the absence of oxygen at the high temperatures and pressures in these steam systems.

Morpholine derivatives used as agricultural fungicides in cereals are known as ergosterol biosynthesis inhibitors

[1] Amorolfine

\[
\begin{align*}
\text{O} & & \text{N} \\
\text{O} & & \text{N}
\end{align*}
\]
Amorolfine (or amorolfin), is a morpholine antifungal drug that inhibits D14 reductase and D7-D8 isomerase \textsuperscript{[36]}, which depletes ergosterol and causes ignosterol to accumulate in the fungal cytoplasmic cell membranes. Marketed as Curanail, Loceryl, Locetar, and Odenil, amorolfine is commonly available in the form of a nail lacquer, containing 5% amorolfine as the active ingredient. It is used to treat onychomycosis (fungal infection of the toe- and fingernails). Amorolfine 5% nail lacquer in once-weekly or twice-weekly applications has been shown in two studies to be between 60% and 71% effective in treating toenail onychomycosis; complete cure rates three months after stopping treatment (after six months of treatment) were 38% and 46%. However, full experimental details of these trials were not available and since they were first reported in 1992 there have been no subsequent trials.

\textbf{[2] Fenpropimorph}

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{N}
\end{array}
\]

Fenpropimorph is a morpholine-derived fungicide used in agriculture, primarily on cereal crops such as wheat.

\textbf{[3] Tridemorph}

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CH}_3
\end{array}
\]

Tridemorph is a fungicide used to control \textit{Erysiphe graminis}. It was developed by BASF in the 1960s who use the trade name Calixin. The World Health Organization has categorised it as a Class II "moderately hazardous" pesticide because it is believed harmful if swallowed and can cause irritation to skin and eyes.
In many commercial drugs also contains Morpholine as a active site which is medicinally active some of these reported here.

[4] **Phenmetrazine**

![Phenmetrazine](image)

Phenmetrazine (Preludin) is a stimulant drug containing a phenethylamine skeleton, in which the terminal amine is incorporated into a morpholine ring, that was previously used as an appetite suppressant, but has since been withdrawn from the market. It was initially replaced by its analogue phendimetrazine which functions as a prodrug to phenmetrazine, but now it is rarely prescribed, due to concerns of abuse and addiction.

[4] **Levofloxacin**

![Levofloxacin](image)

Levofloxacin[^1] (trade names Levaquin (US), Tavanic (EU), and others) is a broad spectrum antibiotic of the fluoroquinolone drug class, and the levo isomer of its predecessor ofloxacin. Its spectrum of activity includes most strains of bacterial pathogens responsible for respiratory, urinary tract, gastrointestinal, and abdominal
infections, including Gram negative (*Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis,* and *Pseudomonas aeruginosa*), Gram positive (methicillin-sensitive but not methicillin-resistant *Staphylococcus aureus, Streptococcus pneumoniae, Staphylococcus epidermidis, Enterococcus faecalis,* and *Streptococcus pyogenes*), and atypical bacterial pathogens (*Chlamydia pneumoniae* and *Mycoplasma pneumoniae*). Compared to earlier antibiotics of the fluoroquinoline class such as ciprofloxacin, levofloxacin exhibits greater activity toward Gram-(+) bacteria but lesser activity toward Gram-(−) bacteria, especially *Pseudomonas aeruginosa*. Levofloxacin and later generation fluoroquinolones are collectively referred to as "respiratory quinolones" to distinguish them from earlier fluoroquinolones which exhibited modest activity toward the important respiratory pathogen *Streptococcus pneumoniae*.

1.3 Research gaps about the novel 2,4,6-tri substituted-1,3,5-triazine derivatives.

   The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side-effects [38]. Therefore, the development of new and different antimicrobial drugs is a very important objective and many research programs are directed the design of new antimicrobial agents.

   As per the review about the derivatization of various 1,3,5-triazine derivatives, it is a six-membered heterocycles containing three nitrogen in the ring and its derivatives have biological activities such as antibacterial, antifungal, antimycobacterial, anti-inflammatory, analgesic, anticancer, antihypertensive, anticonvulsant, antiviral, antidepressant, antiasthmatic, diuretic and hypoglycemic. All these facts were driving force to develop novel 1,3,5-triazine derivatives with wide structural variation. Thus 1,3,5-triazine derivatives plays pivotal role in medicinal chemistry.
Here, we are trying to attached a active compounds like 5-(4-Fluoro-phenyl)-[1,3,4]oxadiazole-2-thiol, 2-Methyl-quinoline-8-amine, 9-ethyl-9H-carbazol-3-amine, 4,5,6,7-Tetrahydro-thieno[2,3-b] pyridine and 4-Amino-N-pyrimidin-2-yl-benzene Sulfonamide with 1,3,5-triazine, which is already part of existing commercial pharmaceuticals. Hence, here we are trying to develop new moiety which having good or better activity then existing pharmaceuticals.

Moreover these substitutions have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. The area in which such a 2,4,6-tri substituted 1,3,5-triazine derivatives has not been reported so far. Hence, it was thought to undertaken such study.

1.4 Objectives of the present work:

In view of above review, the prime objectives of the present thesis are,

- Preparation of various novel 2,4,6-tri substituted-1,3,5-triazine derivatives.
- Evaluation of antimicrobial activity of above prepared heterocycles.
1.5 The present work:

According to the above objectives, research work was carried and distributed into following chapters of the present thesis.

Chapter-2 of the thesis comprises into two sections.
Section-A comprises the details about techniques used for characterization.
Section-B deals with the details about the raw materials used for synthesis. These are as follow.

(i) Cyanuric chloride,
(ii) Amino oxadiazole,
(iii) 2-Methyl-quinoline-8-amine
(iv) 9-ethyl-9H-carbazol-3-amine
(v) 4,5,6,7-tetrahydrothieno[3,2-b]pyridine
(vi) Sulfapyrimidine

Chapter-3 of the thesis comprises the synthesis and characterization of 2-(4-flourophenyl-1,3,4-oxadiazoleyl)-5-thio-4-(morpholino)-6-(arylamino)-s-triazine derivatives.

Chapter-4 of the thesis comprises the synthesis and characterization of N-(9-Ethyl-9H-carbazol-3-yl)-6-morpholin-4-yl-N’-aryl amine-[1,3,5]triazine-2,4-diamine derivatives.

Chapter-5 of the thesis comprises the synthesis and characterization of N-(2-Methyl-quinolin-8-yl)-6-morpholin-4-yl-N’-aryl amine-[1,3,5]triazine-2,4-diamine derivatives.
Chapter-6 of the thesis comprises the synthesis and characterization of [4-(5,6-Dihydro-4H-thieno[2,3-b]pyridin-7-yl)-6-morpholin-4-yl-[1,3,5]triazin-2-yl]-phenyl-amine derivatives.

Chapter-7 of the thesis comprises the synthesis and characterization of 4-(4-Morpholin-4-yl-6-phenylamino-[1,3,5]triazin-2-ylamino)-N-pyrimidin-2-yl-benzenesulfonamide derivatives

All the prepared compounds mentioned in chapters-3 to 7 were screened for their antimicrobial activity. The common biospecies have been selected. The results of such study are discussed in chapter-8.

The entire synthetic route is scanned in Scheme 1.1 to 1.5.
2,4,6-Trichloro-[1,3,5]triazine (1) + 5-(4-Fluoro-phenyl)-[1,3,4]oxadiazole-2-thiol (2) → ThF / 10% NaHCO₃ 0-5°C → 2,4-Dichloro-6-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-[1,3,5]triazine (3)

THF / 10% NaHCO₃ 40-45°C → Morpholine

2-Chloro-4-[5-(4-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-6-morpholin-4-yl-[1,3,5]triazine (4)

Dioxane / 10% NaHCO₃ 100-110°C → 2-(4-fluoro phenyl-1,3,4-oxadiazoleyl)-5-thio-4-(morpholino)-6(arylamino)-s-triazine derivatives (6a-j)

Where, R = 4-CH₃, 4-F, 3-Cl-4-F, 4-NO₂, 4-OCH₃, 3-CH₃, 4-Br, 4-OCONH₂, 3-Cl, 4-Cl

Scheme 1.1
Scheme 1.2
2,4,6-Trichloro-[1,3,5]triazine + 2-Methyl-quinolin-8-ylamine

\[
\text{Cl-}N-\text{Cl} + \text{NH}_2\text{-CH}_3 \xrightarrow{\text{THF / 10\% NaHCO}_3; 0-5^\circ\text{C}} \text{NH}_2\text{-CH}_3 \text{Cl-}N-\text{Cl}
\]

(1) 2,4,6-Trichloro-[1,3,5]triazine

(11) 2-Methyl-quinolin-8-ylamine

(12) (4,6-Dichloro-[1,3,5]triazin-2-yl)-(2-methyl-quinolin-8-yl)-amine

THF / 10% NaHCO$_3$
40-45°C

Morpholine

\[
\text{NH}_2\text{-CH}_3 + \text{Morpholine} \xrightarrow{\text{Dioxane / 10\% NaHCO}_3; 100-110^\circ\text{C}} \text{NH}
\]

(13) (4-Chloro-6-morpholin-4-yl-[1,3,5]-triazin-2-yl)-(2-methyl-quinolin-8-yl)-amine

Where, R = H, 2-CH$_3$, 3-CH$_3$, 4-CH$_3$, 2-Cl, 3-Cl, 4-Cl, 2-NO$_2$, 3-NO$_2$, 4-NO$_2$

N-(2-Methyl-quinolin-8-yl)-6-morpholin-4-yl-N'-aryl amine-[1,3,5]triazine-2,4-diamine derivatives

Scheme 1.3
Scheme 1.4
Where, $R = H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2$

Scheme 1.5
1.6 References


[16] Firdous D. Khan, Manjusha V. Yadav and Ashok D. Sagar, Medicinal chemistry research, 23, 2633 (2014).


