International Journal of Medical Science and Applied Biosciences
ISSN: 2536-7331 (Print): 2536-734x (Online)
Volume 3, Number 3, September 2018
http://www.casirmediapublishing.com

THE CHEMISTRY AND MEDICINAL UTILITY OF PHENOTHIAZINE & PHENOXAZINE HETROCYCLES

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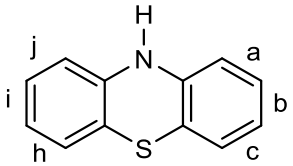
ABSTRACT
From their traditional applications as dyes and pigments, phenothiazines and phenoxazines have gained prominent place in medicine as pharmacological lead structures. This has prompted unprecedented exploratory modification of the parent structures via organic synthesis with a view of synthesizing novel derivatives with improved biological properties. This review underscores various synthetic transformative stages of phenothiazine and phenoxazine scaffolds.

Keywords: phenothiazine, phenoxazine, azaphenothiazine, azaphenoxazine, benzophenothiazine, benzophenoxazine, antipsycotic, antimicrobial, anticancer.

The chemistry of phenothiazine **1** [1-3] and phenoxazine **2** [4-6] has been of great interest to chemists over a century because of their diverse applications in industry and medicine.



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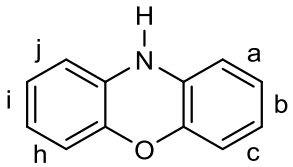

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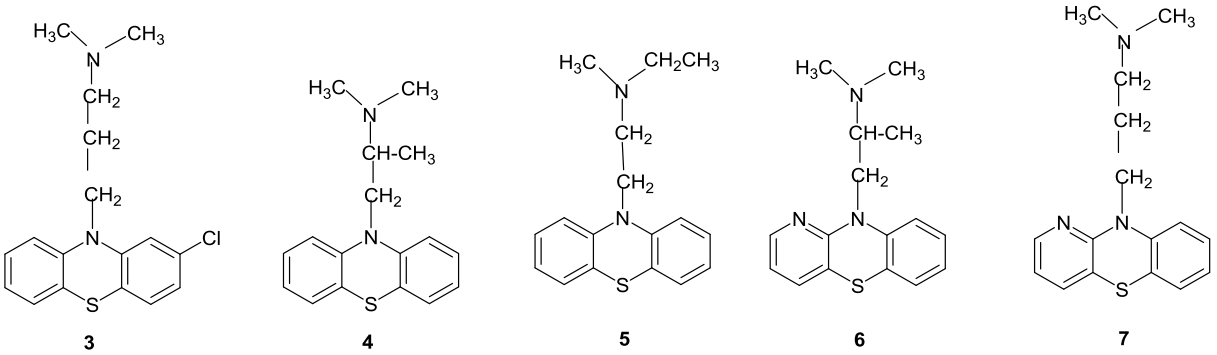
These compounds were first prepared by Bernthsen in 1883 and 1887 by the thionation of diphenylamine and the thermal condensation of *o*-aminophenol with cathecol respectively[7,8]. Originally, they were mainly applied as dyes and pigment in industry but with time they found wider application as antioxidant in lubricant and fuel[9-11], polymerization stabilizers[12-14] , pesticides/insecticides [15-18], biological stains or labellings[19-21], acid-base indicators[22] , and chiefly as drugs , among others. As a result of repeated reports on the pharmacological properties of phenothiazines and phenoxazines, attention was shifted from the study of their dyeing properties to that of their biological properties[23,24]. Phenothiazine and phenoxazine tri-heterocyclic molecules provide the basic structures for various classes of pharmacotherapeutic agents with broad spectrum of biological activities[25,26]. Recent reviews and reports on the progress of biological activities of various synthesized phenothiazines disclosed that they exhibit promising anti-bacterial, anti-fungal, anti-cancer, multidrug resistance reversal(MDR), anti-inflammatory, and anti-viral , antifilarial properties[25,26]. Moreover, studies disclosed that they have trypanocidal, anticonvulsant, analgesic, immunosuppressive, and antimalarial activities[27-34]. Ohlow and Moosmann in Drug Discovery Today opined, 'luck, ingenuity and straightforward chemistry

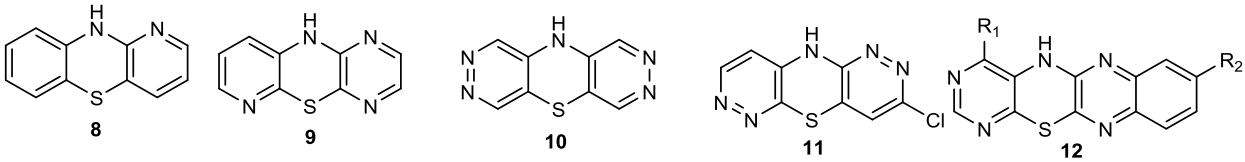
have made phenothiazines the most promiscuous lead structure of the 20th century- and there is more on the horizon'. Interestingly, most of the biological activities of phenothiazines are closely exhibited by phenoxazine and its derivatives as well. For example, novel water soluble 2-amino-4,4a,7-dimethyl-3*H*-phenoxazine was reported to possess antiproliferative, immunosuppressive, antibacterial and antiviral effects[35,36]. In addition multidrug resistance (MDR) modulator in cancer cell of phenoxazines has been reported in several papers[37-40]. Previously phenothiazines and phenoxazines groups of drugs were known as antipsychotic drugs while phenothiazine derivatives and in particular chlorpromazine **3**, promethiazine **4** and diethiazine **5** were applied as tranquilizers, antihistamines and for the treatment of parkinson disease respectively[41,42a].



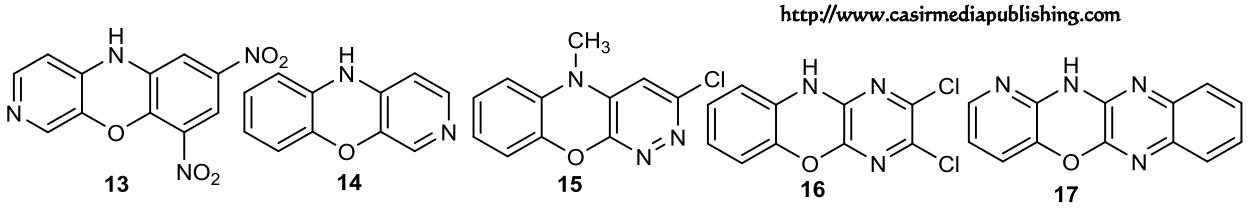
Compounds **3** - **7** were amongst the earlier modification of the structure of the parent compound where attachment of alkylaminoalkyl groups at position-10 of the ring resulted in improved biological activities of the compounds. In addition, the syntheses of aza analogues of compound **1** and **2** were reported[42b,c]. Prominent among them is isothiphendyl **6**, which is a better antihistamic agent than promethiazine and prothipendyl **7** which is a more suitable drug for the treatment of acute psychosis compared to chlorpromazine.

LINEAR PHENOTHIAZINE AND PHENOXAZINE

These discoveries triggered interest in the synthesis of numerous azaphenothiazines[41] of which compounds **8** – **12** are amongst the known ones[43-45].



Pluta, et al (2009) reported immunosuppressive or anticancer activities of twenty three newly synthesized azaphenothiazines in human and mouse models[46,47].
Similarly, the synthesis of several azaphenoxazines has been reported[5,48] of which compounds **13** – **17** are amongst the known ones.

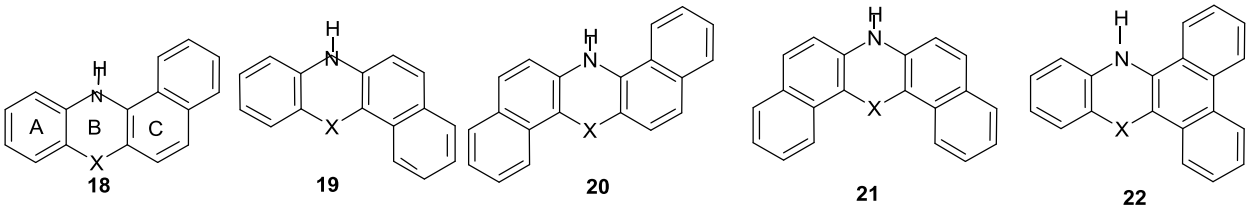


13 **14** **15** **16** **17**

Report on the interesting pharmacological activities of 3,4-diazaphenoxazine **15** prompted the synthesis of other isomeric diazaphenoxazines[48].

NON-LINEAR PHENOTHIAZINE

Further derivitization of compound **1** and **2** in which benzene rings were fused to the sides of ring A and/or C gave non-linear or angular phenothiazine and phenoxazine rings of which benzo[a]phenothiazine and benzo[a]phenoxazine **18**, benzo[c]phenothiazine and benzo[c]phenoxazine **19** , dibenzo[a,h]phenothiazine and dibenzo[a,h]phenoxazine **20**, and dibenzo[c,h]phenothiazine and dibenzo[c,h]phenoxazine **21**; and 14*H*-dibenzo[a,c]phenothiazine and 14*H*-dibenzo[a,c]phenoxazine **22** were among the known ones[3,6,20b,49-52].

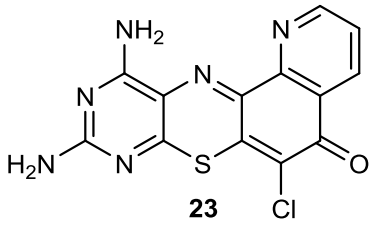


18 **19** **20** **21** **22**

Where X = S or O

It is worthy of note that various derivatives of compounds **18** have been reported as particularly possessing interesting multidrug resistance (MDR) modifying property which is important in cancer chemotherapy and antimicrobial treatment[53-57a-c]. In addition, considerable number of aza derivatives of compounds **18** which should be potentially more pharmacologically active than their carbocyclic analogs were known but their biological properties were largely unknown. Kang and coworkers[58] achieved the synthesis of monoaza-5*H*-benzo[a]phenothiazin-5-ones and benzo[a][1,4]diazabenzothiazino[3,2-c]phenothiazin-5-one by acid catalyzed reaction of substituted 1,4-naphthoquinone with *o*-aminoheterocyclic thiones in alcoholic solution. Okafor[59] reported the syntheses of 11-amino-6-chlorobenzo[a]-8-azaphenothiazin-5-one,11-amino-6-chlorobenzo[a]-8,10-diazaphenothiazin-5-one and 8-amino-6-chlorobenzo[a]-9,11-diazaphenothiazin-5-one[60], while Seiko Nan'ya and his co-workers[61] described the syntheses of 11-aza 5*H*-benzo[a]phenoxazin-5-one,11-aza-5*H*-pyrido[2,3-a]phenoxazin-5-one,11-aza-5*H*-pyrido[3,2-a]phenoxazin-5-one and many of their derivatives. In addition Okoro and his group have reported the synthesis of 1, 8-diaza-5*H*-benzo[a]phenothiazin-5-one[62], 10-methyl-1,11-diaza-5*H*-benz[a]phenothiazin-5-one[63] and 1,11-diaza-5*H*-benzo[a]phenothiazin-5-one[64].

Added to these list is the report of the first synthesis of triazabenzophenothiazine and triazabenzophenoxazine[65,66]; namely, 9,11-diamino-1,8,10-triaza-5*H*-benzo[a]phenothiazin-5-one and 11-amino-1,8,10-triaza-5*H*-benzo[a]phenoxazin-5-one and their anilino derivatives.



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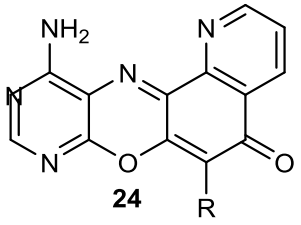

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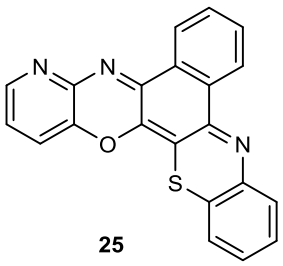
TRIANGULAR PHENOTHIAZINE AND PEHENOZAZINE

In addition, the synthesis of branched intensely coloured and high melting points benzoxazinophenothiazine heterocycles were described[67a]. These compounds are benzo[a][1,4]benzoxazino[3,2-c]phenothiazine **25** which was obtained by treatment of 6-chlorobenzo[a]phenoxazin-5-one with *o*-aminothiophenol in the presence of anhydrous sodium carbonate, 16-oxa-15-thia-4,5,10,14-tetraazabenzo[h]pentaphene **26**, and 4-amino-16-oxa-15-thia,4,5,10,12,14-pentaazabenzo[h]pentaphene **27**. Another example of this class of compounds reported was 14-amino-11,13-diazabenzo[a][1,4]benzoxazino[3,2-c]phenothiazine **28** were prepared by base-catalyzed condensation of 4,6-diaminopyrimidine-5-thiol with 6-chlorobenzo[a]phenoxazine in non-aqueous medium[67b].



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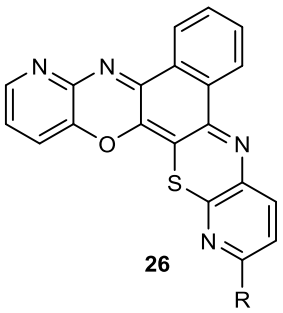

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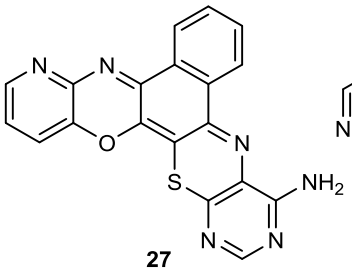

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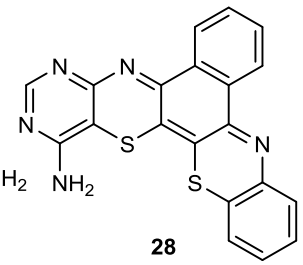

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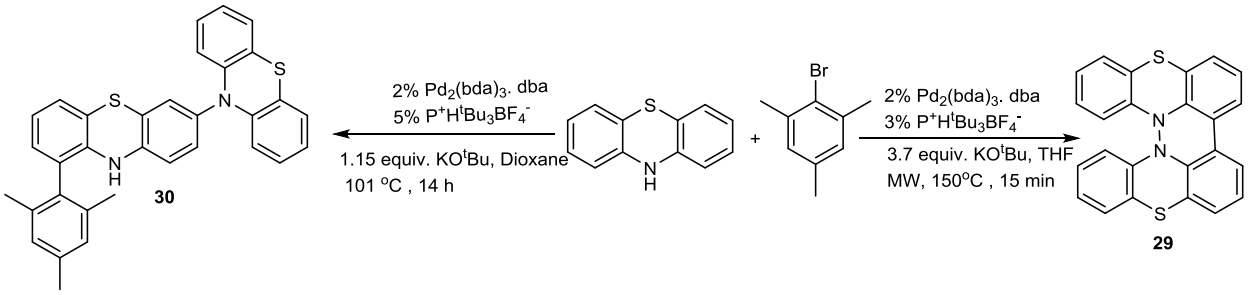
DERIVATIZATION OF PHRNOTHIAZINE AND PHENOXAZINE VIA METAL CATLAYZED SYNTHESIS

We noted like Burgess and Jose in their review of benzophenoxazine-base fluorescent dyes for labeling biomolecules that most of the methods for the synthesis of phenothiazines and phenoxazines are based on classical procedures[68]. However, recently the synthesis of derivatized phenothiazines employing modern organic protocol has emerged. Franz, Romminger and Burgess reported unexpected synthesis of 7,16-diathia-11b,11c-diazabenzo[a,o]perylene **29** and 9-(2,4,6-trimethylphenyl)-10*H*-[3,10′]biphenylthiazynyl **30** by employing Buchward-Hartwig conditions[69].



This perhaps is the first time functionalization of these classes of heterocycles were executed employing this protocol and should encourage researchers in further derivatization of these compounds.

ACKNOWLEDGMENTS

We thank Petroleum Technology Development Funds (PTDF) for financial support and Cardiff University for a short-term research opportunity.

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