Scholars Academic Journal of Biosciences (SAJB)
Sch. Acad. J. Biosci., 2014; 2(4): 255-261
©Scholars Academic and Scientific Publisher
(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com
ISSN 2321-6883 (Online)
ISSN 2347-9515 (Print)
DOI: 10.36347/sajb.2014.v02i04.003

Review Article

Methods for the synthesis of symmetrical and unsymmetrical benzoporphyrins (A review)

Sweta Mishra* and Shive Murat Singh Chauhan
Department of Chemistry, University of Delhi, Delhi-110007, India

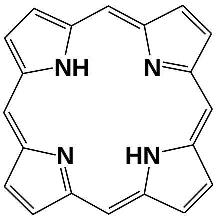
***Corresponding author**
Sweta Mishra
Email: sweta.chem19@gmail.com

Abstract: Benzoporphyrin derivatives have an enormous potential for application in natural and applied sciences. They act as excellent model for photosynthetic reaction center. They are an intermediate between porphyrins and phthalocyanines. Synthesis of benzoporphyrins have remained a big challenge in the field of research. Various synthetic methodologies are used in the past thirty to forty years, several advances have been developed to overcome the previously used procedure. This review is intended to cover the important synthetic utility of TBPs.

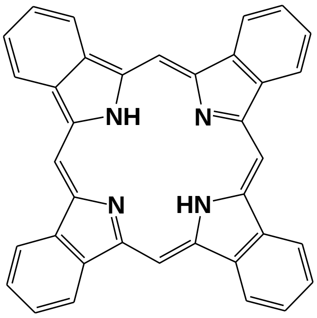
Keywords: Benzoporphyrins; isoindoles; Diels-Alder reaction; CH acids

INTRODUCTION

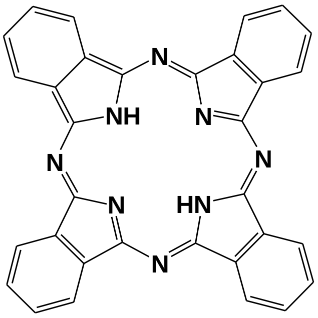
Porphyrin and their complexes have received considerable attention, because of their interesting excited state chemical properties, electron-transfer processes, biological processes, photo-physics and catalytic behaviours [1]. Porphyrins exist in various states in nature and act as centres of energy transfer and charge transfer processes. In nature, the photosynthetic reaction centers perform multistep electron transfer processes with high quantum efficiency and long lifetimes of the final charge separated states of around 1s [2]. From the structural point of view, the simplest representative of this class, tetrabenzoporphyrin (TBP), is an intermediate between “regular” nonextended porphyrins and phthalocyanines, partially retaining properties of both and providing a useful point in structure/property comparative studies. Tetrabenzoporphyrins have been studied substantially more than other extended porphyrins. Their unique photophysical [3,4], optoelectrochemical [5,6] and other physicochemical properties [7,8] have attracted interest in different areas.



Porphyrin



Benzoporphyrin



Phthalocyanine

The tetrabenzoporphyrins and related compounds have been the subjects of extensive studies as agents for PDT [9] optical limiters [10] and other types of nonlinear optical materials [11] luminescent markers for oxygen [12] and pH [13] in biomedical imaging, etc.

Benzoporphyrin acts as a photochemical hole-burning material, since it gets oxidized easily than other porphyrins due to enlargement of π-conjugated system; therefore, it becomes a better photochemical hole-burning material. The synthesis and properties for photosynthetic reaction center model compounds was a subject of intensive research [14-16]. Because the electronic spectrum of benzoporphyrin is similar to that of chlorophyll [17], benzoporphyrin may become a better model compound of the photosynthetic reaction center than tetraphenylporphyrin.

Compared to regular porphyrins and phthalocyanines, the chemistry of tetrabenzoporphyrins and related compounds has been little investigated. The *meso*-substituted tetrabenzoporphyrins are now intensively studied. However, studies on the properties and applications of these macrocyclic compounds have often been faced with difficulties because of the low solubility in common organic solvents [18] and the poor compatibility with polymeric materials. These solubility problems may be overcome by introducing meso-substituents as in the case of porphyrin, the solubility of which is improved by tetraphenyl-substitution at the meso-positions.

The symmetrical and unsymmetrical benzoporphyrins can be synthesized by different approaches. Approaches to the TBP system [19] can be divided as follows.

Low-temperature synthetic approaches

The first approach mimics the standard porphyrin synthesis, i.e., condensation of pyrroles with *meso*-carbon donors. This includes low-temperature synthetis of tetrabenzoporphyrins by the condensation of aromatic aldehydes with isoindole synthons where the benzene ring is present in the latent form. The subsequent disclosure via retro-Diels-Alder reaction [20-22] or oxidation [23] is accomplished after formation of porphyrin ring (Scheme 1). However, the corresponding isoindole synthons (e.g., tetrahydroisoindoles) are fairly unstable and difficultly accessible. So the use of such unstable synthons should be avoided. To overcome such problem another approaches were given in which use of bicyclooctadiene-fused pyrrole were oxidized by thermal retro-Diels-Alder reaction [24]. But these methods still suffered from a common serious drawback, which was the harsh conditions required for the aromatization step (either prolonged heating of metallated hexadecahydroTBP precursors with DDQ leading to partial overoxidation in the tetrahydroisoindole method, or heating over 200 °C to effect ethylene extrusion). Thus, the scope of these approaches was limited, which resulted in losses of valuable target porphyrins at the final stage of a long synthesis. Use of 4,7-dihydroisoindole which is a sofar- unknown simple pyrrole derivative as the precursor for the synthesis of TBPs led to the spontaneous aromatization of annelated rings and allow the mild reaction conditions of the final aromatization step [25]. Ito et al proposed the synthesis of *meso*-Chlorinated bicyclo[2.2.2]octadiene-fused porphyrins by chlorination of the free base TBCODP-H_2 using *N*-chlorosuccinimide (NCS) followed by thermal retro-Diels-Alder reaction [26].

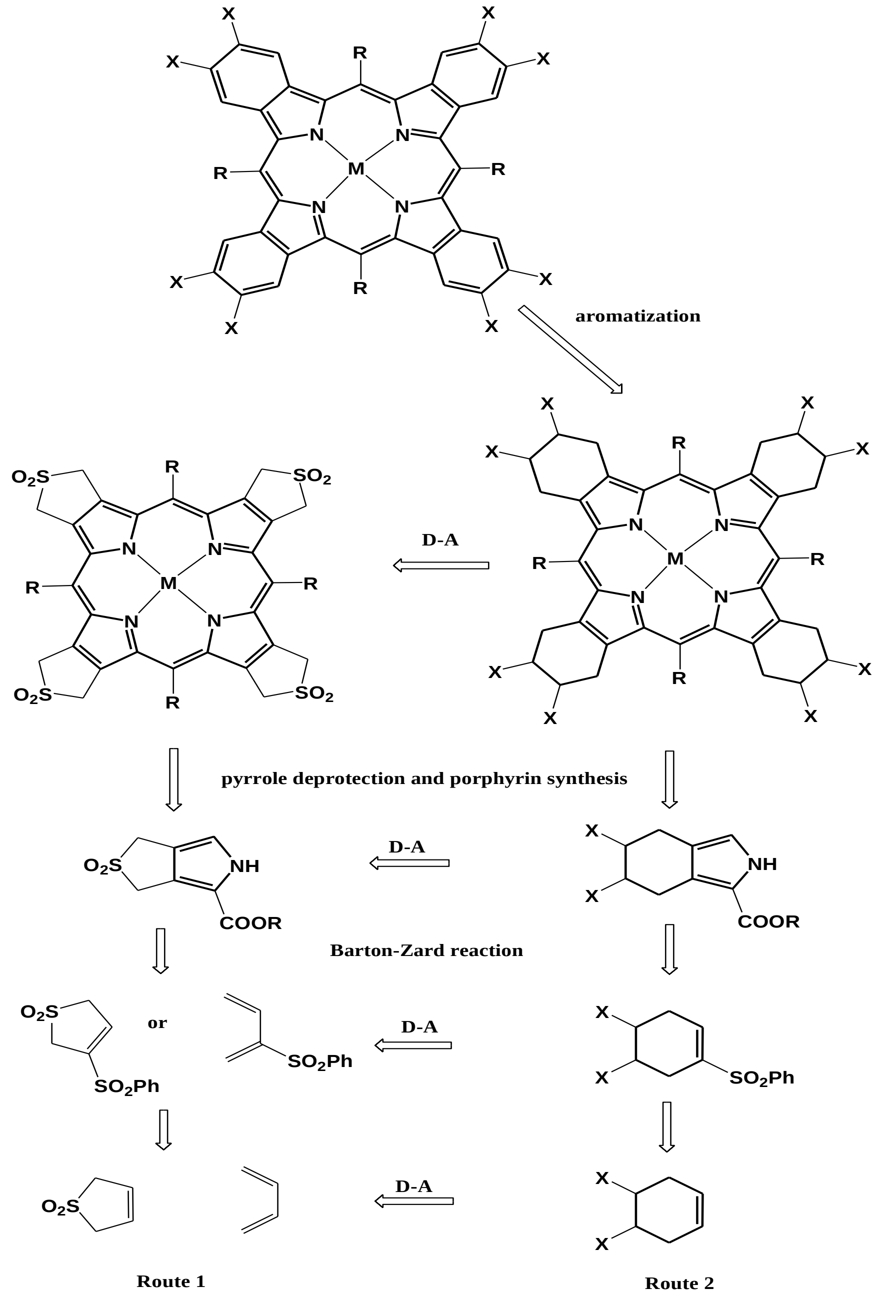
High temperature assisted template directed synthetic approach:

First representatives of this group of compounds were reported in 1981 by Kopranenkov *et al* [27] who synthesized the zinc complex of *meso*-tetraphenyltetrabenzoporphine from phthalimide and phenylacetic acid in the presence of zinc acetate. The authors assumed formation of partially *meso*-substituted products also, i.e., zinc complexes of mono-, di-, and triphenyltetrabenzoporphines. Since the reaction mixture consists of acetate ion as a source of methylene component which explained the formation of side products. Later on, the synthesis of *meso*-phenyl-substituted tetrabenzoporphines was studied in detail by Ichimura *et al* [28] By fusion of potassium phthalimide with zinc phenylacetate at 360 ^{o}C for 1 h; the authors obtained a mixture of zinc complexes of *meso*-phenylsubstituted tetrabenzoporphines.

Moreover, the nature of such precursors and the possibility for further transformations restricts the number of substituents that could be introduced. The second group of methods, which subsequently led to a much wider array of TBP's, stemmed from basic phthalocyanine synthesis[3,29-30] In these methods the *meso*-carbons in the porphyrin skeleton come not from electrophilic carbonyls, as in traditional porphyrin condensations (Rothmund/Adler-Longo/Lindsey), but from nucleophilic CH acids. As a result, unstable isoindoles can be replaced by readily available phthalimides or their derivatives. One version of this approach, developed by Lukyanets and co-workers [31], appeared useful for the synthesis of Ar_4TBP's. According to their method, phthalimide is condensed with CH acids (e.g. arylacetic acids) in the presence of metal salts, which act as templates (Scheme 2 & 3).

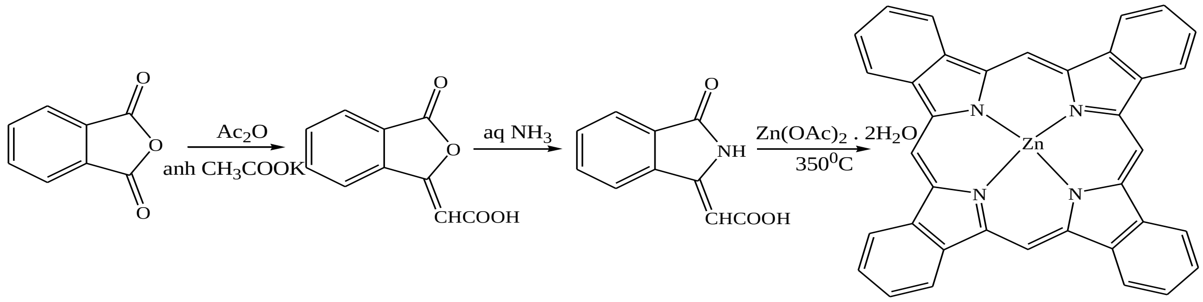
However, the conditions required for the condensation were so harsh (fusion at 350-400 °C) that only inert substituents in the starting materials, such as alkyl or halogen could sustain the procedure.

Zinc complexes of *meso*-tetraalkyltetra benzoporphyrins were synthesized for the first time in 1984 following a three-step procedure utilizing monoalkylmalonic acids as starting compounds [32]. However, the large number of steps and low accessibility of the initial reagents stimulated search for more practical methods for the synthesis of *meso*-tetraalkyltetrabenzoporphyrins. It is known that metal complexes of *meso*tetraaryltetrabenzoporphyrins can be obtained by template condensation of phthalimide with excess arylacetic acid in the presence of zinc(II) hydroxide[33]. To synthesize zinc complexes of *meso*-tetraalkyltetrabenzoporphyrins in such a way, i.e., by reaction of phthalimide with excess aliphatic carboxylic acid zinc salt, were successful only in the case of lower carboxylic acids, propionic and butyric, while the reactions with zinc(II) octanoate, decanoate, and octadecanoate failed. Presumably, the reason is that it was impossible to attain sufficiently high temperature (320–330°C) which was necessary to complete the process because of the low boiling point of the reaction mixture (250–270°C). Various derivatives of TBPs such as alkyl, alkyloxy, aryl and triphenyl aryloxy TBPs have been synthesized via this method [34-35]

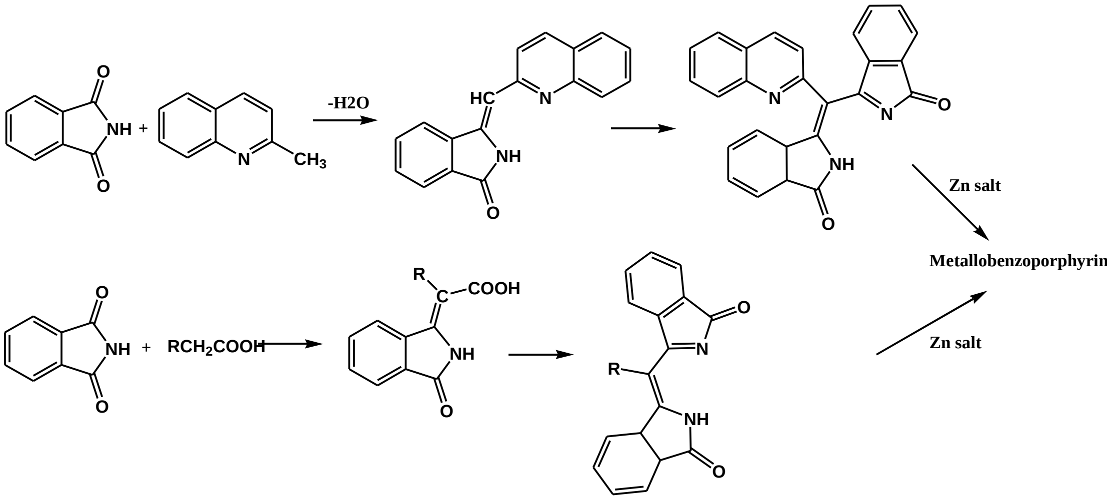


D-A denotes Diels-Alder reaction

Scheme 1: Reterosynthetic analysis of TBP systems



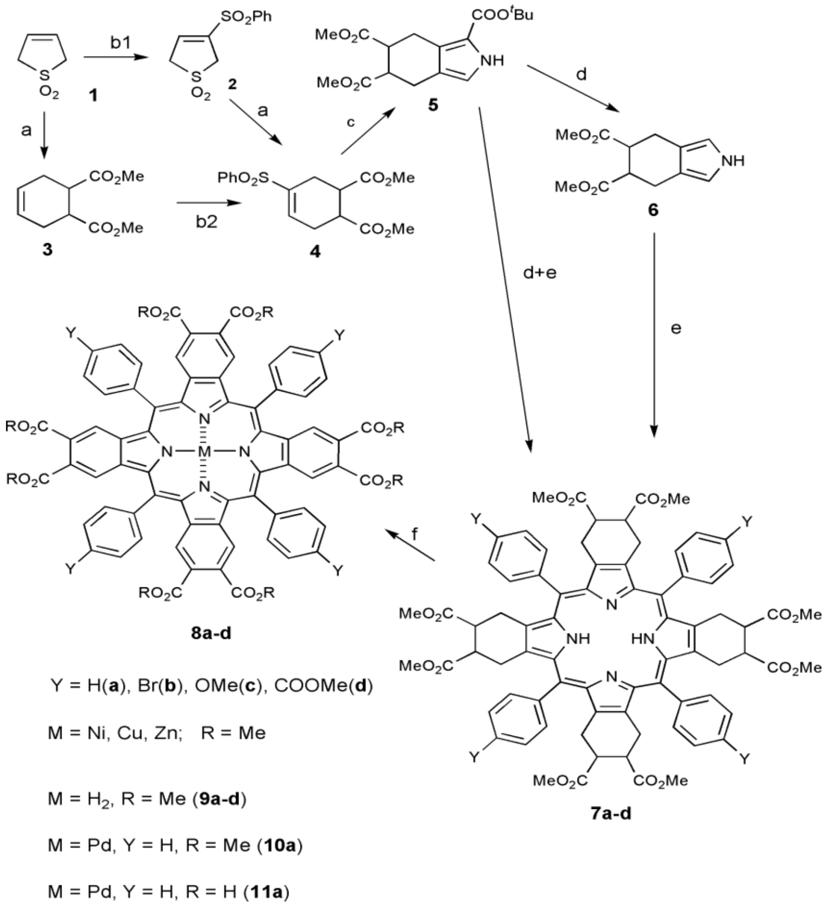
Scheme 2: Synthesis of benzoporphyrins



Scheme 3: Synthetic pathway for TBP via this approach

Synthetic approach of unsymmetrical tetrabenzoporphyrins

The available information on unsymmetrical tetrabenzoporphyrins is concerned mainly with *meso*-aryl-substituted derivatives [36-38] while those having no substituents in the *meso* positions have been studied to a considerably lesser extent. Monobenzoporphyrin and its metal complexes (which were detected for the first time in oil [39] and were then prepared by synthetic methods [40] may be regarded as first representatives of that group of compounds. The procedure proposed [41] is based on the Diels–Alder reaction of protoporphyrin IX dimethyl ester with dimethyl acetylenedicarboxylate, followed by elimination of the angular methyl group from the adduct. However, this procedure has a limited applicability; therefore, Sapunov et al [42] later proposed to obtain unsymmetrical benzoporphyrins by joint condensation of imides derived from two different *ortho*-dicarboxylic acids.



Y = H(**a**), Br(**b**), OMe(**c**), COOMe(**d**)

M = Ni, Cu, Zn; R = Me

M = H_2, R = Me (**9a-d**)

M = Pd, Y = H, R = Me (**10a**)

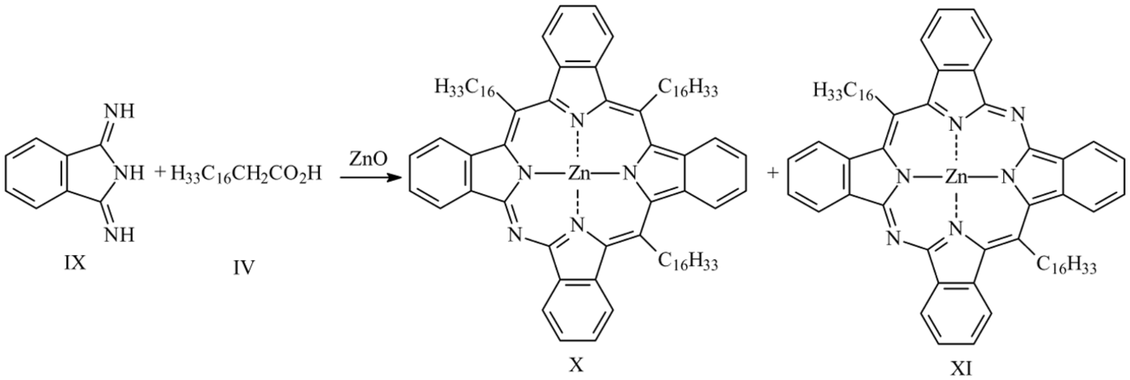
M = Pd, Y = H, R = H (**11a**)

Scheme 4: *Reagents and conditions*: a, DMM, Py, 140 °C, pressure tube, 85%; b1, (i) PhSCl. CH_2Cl_2; (ii) Et_3N; (iii) Oxone, MOH, 86% for three steps; b2, (i) PhSCl, CH_2Cl_2; (ii) MCPBA; (iii) DBU, 81% for three steps; c, $CNCH_2CO_2$ tBu, tBuOK, THF, Ar, 0 °C, 80–95%; d, TFA– CH_2Cl_2, Ar, rt, 35–40%; e, (i) Y = C_6H_4CHO, BF3·Et2O, CH_2Cl_2; (ii) DDQ, 25–35% for two steps; d + e, Y = C_6H_4CHO (X = H), AcOH, TosOH, CH_2Cl_2, 8–12%; f, (i) $M(OAc)_2$, MeOH–$CHCl_3$; (ii) DDQ, THF or MeCN, reflux, M = Zn, Cu, Ni, 98% for two steps

Gottumukkala et al synthesized water-soluble nido-carboranyl-TBP in six steps and 43% overall yield from butanopyrrole and carboranylbenzaldehyde using above mentioned approach [43].

A drawback of this method is that the reaction gives a mixture of porphyrins which are often difficult to separate on a preparative scale. The most reasonable procedure for the synthesis of unsymmetrical benzoporphyrins is likely to be stepwise condensation [44]. It is known that structurally related unsymmetrical porphyrazines containing both electron-donor and electron-withdrawing substituents and possessing a high dipole moment are very promising for use in various fields of science and techniques.

Aza-derivatives of meso-alkyl substituted tetrabenzopophyrines have been synthesized in literature with the purpose to determine the influence of nitrogen atoms in meso-positions of the tetrabenzoporphyrine macrocycle on the physico-chemical properties of porphyrines [45].



Scheme 5: Aza-derivatives of meso-alkyl substituted tetrabenzopophyrines

The molecular structure of the metallo-tetrabenzoporphyrins and H_2TBP are as follows. Benzene rings attached to the pyrroles provide the structural similarity of the tetrabenzoporphyrins to the phthalocyanines. The symmetric structure of MgTBP and ZnTBP puts them in the point group D_{4h}. According to Gouterman, the four-orbital model predicts a degenerate $S_0 \rightarrow S_1$, transition (Q band) and a degenerate $S_0 \rightarrow S_2$, transition (Soret or ***B*** band), where both transitions are localized in the molecular plane [46]. The strong Soret and Q bands arise in part from the delocalized nature of the π-electrons shared by the 18 or 16 conjugated bonds in the ring. The Q transition is made possible by configuration interaction mixing. The addition of the benzo groups to the basic porphyrin ring presumably plays an important role in the nature of the bands. The increased size of the TBPs over the basic porphyrin ring results in a predicted red shift of the Soret and Q bands by about 50 nm, utilizing the modified free electron molecular orbital method [47].

CONCLUSIONS

We have described the various synthetic approaches for tetrabenzoporphyrinoids. Above all mentioned methodology two major approaches came into light, one is low temperature and another is high temperature method. However high temperature is a harsh condition and gives rise to several side products but it is a one pot condensation while synthesis at low temperature includes number of steps which further reduces the yield of desired product. So synthesis of TBP is still a challenging field for researchers.

REFERENCES

1. Diesenhofer J, Michel H; The Photosynthetic Reaction Center from the Purple Bacterium Rhodopseudomonas viridis, Angew. Chem. Int. Ed., 1989; 28: 829-847.
2. McDermott G, Prince SM, Freer AA, Hawthornethwaite-Lawles AM, Papiz MZ, Cogdell RJ, Isaacs NW; Crystal structure of an integral membrane light-harvesting complex from photosynthetic bacteria, Nature, 1995; 374: 517.
3. Koehorst RBM, Kleibeuker JF, Tjeerd JS, de Bie DA, Geursten B, Henrie RN, van der Plas HC; Preparation and spectroscopic properties of pure tetrabenzoporphyrins, J. Chem. Soc. Perkin Trans 2, 1981; 1005-1009.
4. Nguyen KA, Pachter R; Ground state electronic structures and spectra of zinc complexes of porphyrin, tetraazaporphyrin,

tetrabenzoporphyrin, and phthalocyanine: A density functional theory study, J. Chem. Phys., 2001; 114: 10757-10767.

5. Madoka Y, Tsiguo Y, Osami O, Kunihiro I, Hisayuki M, Masako S, Optical and redox properties of meso-diphenyltetrabenzoporphyrins, Inorg. Chim. Acta, 1991; 185 (1): 39-47.
6. Plagemann B, Renge I, Renn A, Wild UP; Spectroscopy and photochemistry of meso-diphenyltribenzonaphthoporphyrin at low temperatures: a novel system for hole-burning applications, J. Phys. Chem. A, 1998; 102: 1725-1732.
7. Bonnet R, Martinez G; Photobleaching studies on azabenzoporphyrins and related systems: a comparison of the photobleaching of the zinc(II) complexes of the tetrabenzoporphyrin, 5-azadibenzo(b,g)porphyrin and phthalocyanine systems, J. Porph. Phtha., 2000; 4: 544-550.
8. Finikova OS, Cheprakov AV, Carroll PJ, Dalosto S, Vinogradov SA; Influnce of nonplanarity and extended conjugation on porphyrin basicity, Inorg. Chem., 2002; 41 (26): 6944-6946.
9. Friedberg JS, Skema C, Baum ED, Burdick J, Vinogradov SA, Wilson DF, Horan AD, Nachamkin I; In vitro effects of photodynamic therapy on Aspergillus fumigatus, J. Antimicrob. Chemother., 2001, 48 (1): 105-107.
10. Ono N, Ito S, Wu CH, Chen CH, Wen TC; Nonlinear light absorption in meso-substituted tetrabenzoporphyrin and tetraarylporphyrin solutions, Chem. Phys., 2000, 262 (2-3): 467-473.
11. Karotki A, Drobizhev M, Kruk M, Spangler C, Nickel E, Mamardashvili N, Rebane A; Enhancement of two-photon absorption in tetrapyrrolic compounds, J. Opt. Soc. Am. B-Opt. Phys., 2003, 20: 321-332.
12. Rietveld IB, Kim E, Vinogradov SA, Dendrimers with tetrabenzoporphyrin cores: near infrared phosphors for in vivo oxygen imaging, Tetrahedron, 2003, 59 (22): 3821-3831.
13. Finikova O, Galkin A, Rozhkov V, Cordero M, Hagerhall C, Vinogradov S; Porphyrin and tetrabenzoporphyrin dendrimers: tunable membrane-impermeable fluorescent pH nanosensors, J. Am. Chem. Soc., 2003, 125 (16): 4882-4893.
14. Wasielewsk MR; Photoinduced electron transfer in supramolecular systems for artificial photosynthesis, Chem. Rev., 1992, 92 (3): 435-461.
15. Gust D, Moore TA, Makings LR, Liddell PA, Nemeth GA and Moore AL; Photodriven electron transfer in triad molecules: a two-step charge-recombination reaction, J. Am. Chem. Soc., 1986, 108 (25): 8028-8031.
16. Sakata Y, Tsue H, O'Neil MP, Wiederrecht GP, Wasielewaski MR; Effect of donor-acceptor orientation on ultrafast photoinduced electron transfer and dark charge recombination in porphyrin-quinone molecules, J. Am. Chem. Soc., 1994, 116: 6904-6909.
17. Dolphin D; The Porphyrins; Academic Press:New York, 1978: 3, 1.
18. Vogler A, Kunkely H; Simple template synthesis of zinc tetrabenzoporphyrin Angew. Chem., 1978, 17 (10): 760.
19. Lash TD, Synthesis of novel porphyrinoid chromophores, In The Porphyrin Handbook; Kadish KM, Smith KM, Guilard R; Eds. Academic Press: New York, 2000; Chapter 10.
20. Vicente MGH, Tome AC, Walter A, Cavaleiro JAS; Synthesis and cycloaddition reactions of pyrrole-fused 3-sulfolenes: a new versatile route to tetrabenzoporphyrins, Tetrahedron Lett., 1997, 38 (20): 3639-3642.
21. Ito S, Ochi N, Murashima T, Uno H, Ono N; A new synthesis of benzoporphyrins using 4,7-dihydro-4,7-ethano-2H-isoindole as an isoindole equivalent, Heterocycles, 2000, 52 (1): 399.
22. Uno H, Ishikawa T, Hoshi T, Ono N; Soluble precursors convertible to tetrabenzoporphyrins below room temperature, Tetrahedron Lett., 2003, 44 (28): 5163-5168.
23. Finikova OS, Cheprakov AV, Beletskaya IP, Carroll PJ, Vinogradov SA; Novel Versatile Synthesis of Substituted Tetrabenzoporphyrins J. Org. Chem., 2004, 69, 2 (2) 522-535.
24. Yamada H, Kushibe K, Okujima T, Uno H, Ono N; Novel one-pot synthesis of 5-alkenyl-15-alkynylporphyrins and their derivatisation to a butadiyne-linked benzoporphyrin dimer, Chem. Commun., 2006, 383-385.
25. Filatov MA, Cheprakov AV, Beletskaya IP; A Facile and Reliable Method for the Synthesis of Tetrabenzoporphyrin from 4,7-Dihydroisoindole, Eur. J. Org. Chem., 2007, 3468-3475.
26. Ito S, Phong LT, Komatsu T, Igarashi N, Otsubo S, Sakai Y, Ohno A, Aramaki S, Tanaka Y, Uno H, Oba T, Hiratani K; First Synthesis of meso-Chlorinated Tetrabenzoporphyrins, Eur. J. Org. Chem., 2009, 5373-5382.
27. Kopranenkov VN, Dashkevich SN, Lukyanets EA; Meso-tetraaryltetrabenzoporphines Zh. Obshch. Khim., 1981, 51: 2513-2517.
28. Ichimura K, Sakuragi M, Morii H, Yasuike M, Toba Y, Fukui M, Ohno O; Formation of tetrabenzoporphine skeleton by the reactions of phthalimide with zinc carbonates, Inorg. Chim. Acta, 1991, 186: 95-101.
29. Vogler A, Kunkely H, Rethwisch B; Tetrabenzporphyrin complexes of iron, palladium and platinum, Inorg. Chim. Acta 1980, 46: 101-105.

30. Linstead RP, Weiss FT; Phthalocyanines and related compounds. XX. Further investigations on tetrabenzoporphine and allied substances J. Chem. Soc., 1950, 2975.
31. (a) Kopranenkov VN, Makarova EA, Lukyanets EA; New approach to the synthesis of metallic complexes of tetrabenzoporphines Zh. Obshch. Khim., 1981, 51: 2727-2730 (Russian). (b) Kopranenkov VN, Makarova EA, Dashkevich SN; Novel isoindologens in tetrabenzoporphyrin synthesis, Khim. Geterotsikl. Soedin., 1985, 10: 1372-1377 (Russian). (c) Kopranenkov VN, Makarova EA, Dashkevich SN, Lukyanets EA; Synthesis and electronic absorption spectra of substituted tetrabenzoporphines, Khim. Geterotsikl. Soedin., 1988, 6: 773-779 (Russian).
32. Kopranenkov VN, Dashkevich SN, Shevtsov VK, Lukyanets EA; Synthesis of meso-tetraalkyltetrabenzoporphyrins Khim. Geterotsikl. Soedin., 1984, 1: 61-64.
33. Lukyanets EA, Dashkevich SN, Kobayashi N; Russ. J. Gen. Chem., 1993, 63: 985.
34. (a) Yakubova LA, Galanina NE, Shaposhnikova GP, Lebedevab NS, Mal'kova EA; meso-Tetraalkyltetrabenzoporphyrins and their zinc complexes. synthesis and properties, Russ. J. Gen. Chem., 2008, 78: 1255-1259. (b) Galanin NE, Yakubov LA, Shaposhnikov GP; Synthesis and spectral properties of [3-(heptyloxy)phenoxy]acetic acid and its derived meso-sibstituted tetrabenzoporphyrins, Russ. J. Gen. Chem., 2008, 78: 1802-1807. (c) Khoroshutin AV, Chumakov DE, Anisimov AV, Kobrakov KI; Regioselective bromination of (tetraphenyltetrabenzoporphyrinato) palladium(II). synthesis of a new octabromo derivative of the tetraphenyltetrabenzoporphyrin series, Russ. J. Gen. Chem., 2007, 77: 1959-1964.
35. Galanin NE, Yakubov LA, Shaposhnikov GP, Synthesis and properties of [4-(triphenylmethyl)phenoxy]acetic and 3-[4-(triphenylmethyl)phenoxy]propionic acids and their condensation with phthalimide leading to meso-substituted tetrabenzoporphyrins, Russ. J. Org. Chem., 2009, 45 (7): 1024-1030.
36. Galanin NE, Kudrik EV, Shaposhnikov GP; Synthesis and properties of meso-triphenyltetrabenzoporphine and its zinc complex, Russ. J. Gen. Chem., 2000, 70: 1292.
37. Kudrik EV, Islyaikin MK, Frantseva SV; Synthesis and properties of diphenyltetrabenzoporphine and its metal complexes Russ. J. Gen. Chem., 1997, 67: 1132.
38. Galanin NE, Kudrik EV, Shaposhnikov GP; Synthesis and Properties of meso-Monophenyltetrabenzoporphine and its Zinc Complex Russ. J. Gen. Chem., 2002, 72: 1119.
39. Beker EW, Yen TF, Dickie JP, Rhodes RE, Clark LF; Mass spectrometry of porphyrins. II. Characterization of petroporphyrins, J. Am. Chem. Soc., 1967, 89: 3631-3639.
40. Clesy RS, Mizra AH; The chemistry of pyrrolic compounds. XLIX. Further observations on the chemistry of the benzoporphyrins, Aust. J. Chem., 1982, 35: 197-209.
41. Morgan AR, Pangka VS, Dolphin D; Ready syntheses of benzoporphyrins via Diels-Alder reactions with protoporphyrin IX, J. Chem. Soc. Chem. Commun., 1984, 1047-1048.
42. Sapunov VV, Solovev KN, Kopranenkov VN, Vorotnikov AM; Triplet-triplet absorption spectra of zinc tetranaphthoporphines, Zh. Prikl. Spektrosk., 1986, 45: 56.
43. Gottumukkala V, Ongayi O, Baker DG, Lomax LG, Vicente MGH; Synthesis, cellular uptake and animal toxicity of a tetra(carboranylphenyl)-tetrabenzoporphyrin, Bioorg. Med. Chem. 2006, 14 (6): 1871–1879.
44. Galanin NE, Kudrik EV, Shaposhnikov GP; Stepwise synthesis and spectral characteristics of meso-trans-diphenyldi(1-naphthyl)tetrabenzoporphine and its zinc complex, Russ. J. Org. Chem., 2003, 39: 1183.
45. Bykova1 V, Usoltseva1 N, Kudrik E, Galanin NE, Shaposhnikov GP, Yakubov L; Synthesis and induction of mesomorphic properties of tetrabenzoporphine derivatives, Mol. Cryst. Liq. Cryst., 2008, 494: 38-47.
46. Gouterman M; Spectra of porphyrins J. Mol. Spectrosc. 1961, 6: 138-163.
47. Scherz A, Levanon H; Optical transition energies of porphyrins. The application of free electron molecular orbital approach, Molec. Phys., 1985, 55: 923-937.