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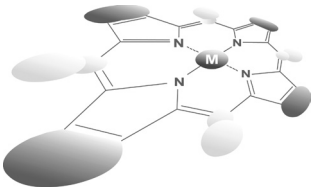

Application of metalloporphyrins as new catalysts for the efficient, mild and regioselective synthesis of quinoxaline derivatives

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ABSTRACT: A simple, highly efficient and green procedure for the condensation of aryl and alkyl 1,2-diamines with α-diketones in the presence of catalytic amounts of metalloporphyrins at room temperature is described. Using this method, quinoxaline derivatives as biologically interesting compounds are produced in high to excellent yields and short reaction times. In this report, the effects of central metal in porphyrin core and substituents on tetraphenylporphyrin skeleton have been studied.

KEYWORDS: metalloporphyrin, quinoxaline, 1,2-diamine, α-diketone, catalyst.

INTRODUCTION

Metalloporphyrins have been the subject of many studies because these complexes show wide applicability and are now used as the catalysts for a variety of photosensitizers [1], redox catalysts [2], hydroxylation and epoxidation of hydrocarbon compounds [3, 4], aziridination of olefins [5], oxidation of sulfides to sulfones [6], hydroxylation of aromatic compounds [7], asymmetric carbon-hydrogen bond formation [8], oxidative carbonylation of amines [9], silylation of hydroxy groups [10] and ring opening of epoxides [11]. Nowadays, finding a new catalytic activity of metalloporphyrins is more fascinating for chemists.

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry as they have various biological activities, such as antimycobacterial [12], antidepressant [13], and antitumor drugs [14]. They have been also used as building blocks for the synthesis of organic semiconductors [15]. Moreover, these compounds have been applied for the preparation of various dyes [16].

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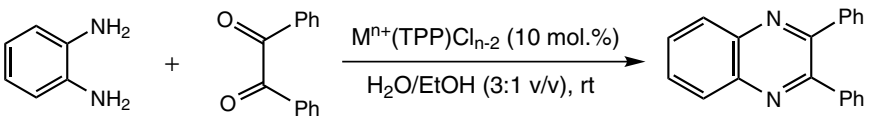
The condensation of 1,2-diamines with 1,2-diketones has been used as a useful protocol for the synthesis of quinoxalines. For this transformation, several catalysts and reagents have been reported, including $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ [17], sulfamic acid [18], oxalic acid [19], polianiline-sulfate salt [20] and iodine in DMSO [21]. Other methods which have been applied for the synthesis of quinoxaline derivatives include heteroannulation of nitroketone N,S-aryliminoacetals with $POCl_3$ [22], bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines [23] and cyclization of α-arylimino oximes of α-dicarbonyl compounds [24]. However, many of the reported protocols are associated with one or more of the following disadvantages: need for anhydrous conditions, harsh reaction conditions, the use of expensive reagents, prolonged reaction times, moderate yields and no agreement with the green chemistry protocols. Therefore, development of an efficient, cheap, simple and environmentally friendly method for the preparation of quinoxaline derivatives is desirable. Furthermore, no catalytic protocol for the synthesis of quinoxalines in the presence of metalloporphyrins has been reported in the literature so far.

In this study, we wish to introduce a novel method for the synthesis of quinoxaline derivatives in the presence of metalloporphyrins as catalyst at room temperature (Scheme 1).



1 2 3a

Scheme 1. Condensation of benzene-1,2-diamine with benzil

Table 1. The reaction of benzene-1,2-diamine (1.1 mmol) with benzil (1 mmol) in the presence of different metalloporphyrins (10 mol %) in EtOH/H_2O (1/3) (4 mL)

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Cr(TPP)Cl	2.0	65
2	Mn(TPP)Cl	3.0	70
3	Fe(TPP)Cl	3.0	70
4	**Co(TPP)Cl**	**1.5**	**75**
5	Co(TPP)	2.5	60
6	Ni(TPP)	2.0	60
7	Cu(TPP)	2.5	55
8	Zn(TPP)	2.5	60
9	TPP	4.0	32
10	_	4.0	25

[a] Isolated yield.

In order to find a suitable catalyst for the synthesis of quinoxalines from 1,2-diamines and α-diketones, the condensation reaction of benzene-1,2-diamine with benzil in the presence of different metalloporphyrins were chosen as a model to provide compound **3a** (Scheme 1). The reactions were studied in EtOH/H_2O (1:3 v/v) at room temperature. The results are displayed in Table 1.

At first, this model reaction were carried out in the presence of the catalytic amount of some metal complexes of tetraphenylporphyrin [$M^{n+}TPPCl_{n-2}$] [M^{n+} = Cr^{3+}, Mn^{3+}, Fe^{3+}, Co^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and TPP = tetraphenylporphyrin dianion] (10 mol %) to examine the effects of the central metal on the catalytic properties of porphyrin in these reaction conditions (Fig. 1). The results are summarized in Table 1. The yield of quinoxaline is controlled by the variation of central metal in porphyrin core. Trivalent metalloporphyrins [Cr^{3+}, Mn^{3+}, Fe^{3+} and Co^{3+}] appear to give better yields of quinoxaline in comparison with divalent metalloporphyrins [Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}]. This reactivity refers to this fact that, trivalent metalloporphyrins are more acceptor than divalent metalloporphyrins. This behavior leads to the increase interaction between metalloporphyrins, diketones and diamines.

According to Table 1, entry 4, Co(TPP)Cl is the most effective catalyst and the reaction was completed in shorter reaction time. In the presence of other metalloporphyrins, the reaction times were longer and the yields of quinoxalines were low. A control with porphyrin free base has been shown in Table 1, entry 9 and these data show that central metal is essential for catalytic activity of porphyrin. Moreover, to clarify the effect of the porphyrin catalyst on the reaction, the model reaction was examined in the absence of the catalyst and the yield of quinoxaline was low after a long time (25% of quinoxaline **3a** after 4 h) (Table 1, entry 10).

Due to the conjugation effect, either electron density or electron withdrawing groups of the *para* positions of four phenyls around the porphyrin rings of the positions of 5, 10, 15 and 20 strongly influence the catalytic activities of metalloporphyrins. To obtain information on the catalytic activities, 12 kinds of Co^{III}-porphyrins catalysts were also examined in the formation of quinoxaline **3a**. According to the results from Table 2, no significant correlation between the electronic effects of substituents on Co(III) porphyrins and their activity for the synthesis of quinoxaline **3a** was observed. Among the catalysts examined, Co(T*p*OMePP)Cl gave the best results. The results are presented in Table 2.

The results of the quinoxaline synthesis by Co(T*p*OMePP)Cl in various protic and aprotic solvents are reported in Table 3. We found that these reactions appeared to be largely dependent on the nature of the solvent and the mixture of H_2O/EtOH (3:1 v/v) is the best medium for these reactions (Table 3, entry 4).

To realize the generality and versatility of the catalyst, different aryl and alkyl 1,2-diamines were condensed with

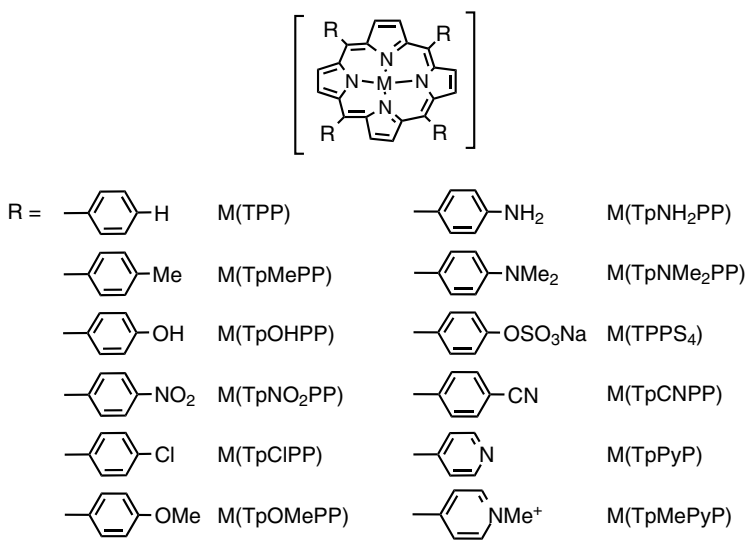


Fig. 1. The structures of metalloporphyrins used in this study

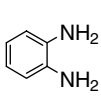
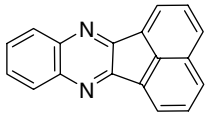
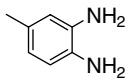
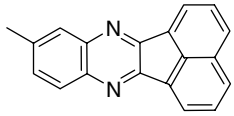
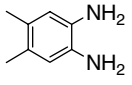
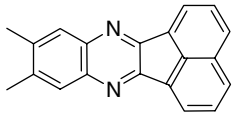
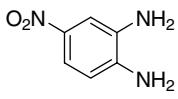
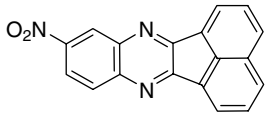
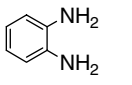
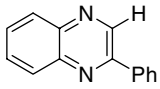
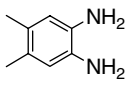
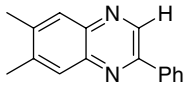
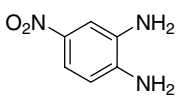
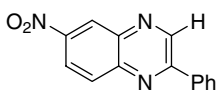
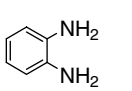
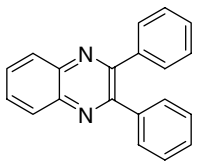
Table 2. Reaction of benzene-1,2-diamine (1.1 mmol) with benzil (1 mmol) in the presence of various cobaltporphyrins (0.1 mmol) as catalysts in EtOH/H_2O (1/3) (4 mL)

Entry	Cobalt(III) porphyrin	Time (min)	Yield (%)
1	Co(TPP)Cl	90	75
2	Co(T*p*MePP)Cl	50	70
3	Co(T*p*OHPP)Cl	300	60
4	Co(T*p*NO_2PP)Cl	50	70
5	Co(T*p*ClPP)Cl	120	70
6	**Co(T*p*OMePP)Cl**	**35**	**80**
7	Co(T*p*NH_2PP)Cl	180	65
8	Co(T*p*NMe_2PP)Cl	120	60
9	Co(T*p*PPS_4)Cl	120	70
10	Co(T*p*PyP)Cl	300	60
11	Co(T*p*MPyP)Cl	300	70
12	Co(T*p*CNPP)Cl	60	65

Table 3. The effect of various solvents (4 mL) on the reaction of benzene-1,2-diamine (1.1 mmol) with benzil (1 mmol) in the presence of Co(T*p*OMePP)Cl (0.1 mmol) at room temperature

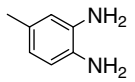
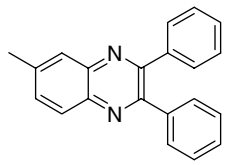
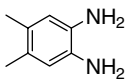
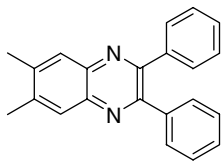
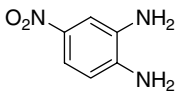
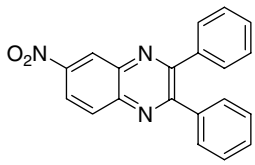
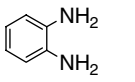
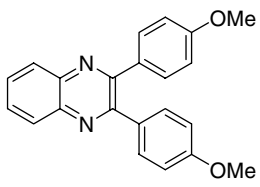
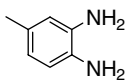
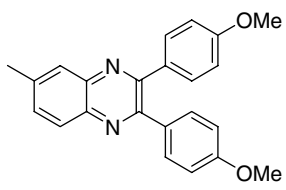
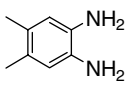
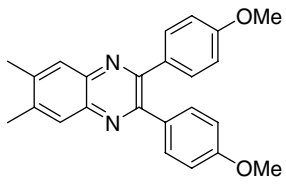
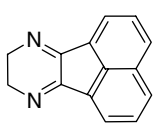
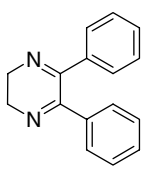
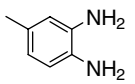
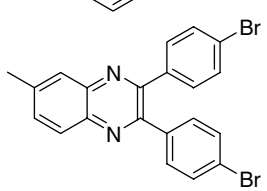
Entry	Solvent	Time (min)	Yield (%)
1	EtOH	120	45
2	EtOH/H_2O (3/1)	120	60
3	EtOH/H_2O (1/1)	40	75
4	**EtOH/H_2O (1/3)**	**35**	**80**
5	H_2O	120	50
6	CH_3CN	120	45
7	$CHCl_3$	120	45
8	ethylacetate	120	45
9	DMF	120	50
10	MeOH	120	50

Table 4. Synthesis of quinoxaline derivatives from 1,2-diamines and α-diketones

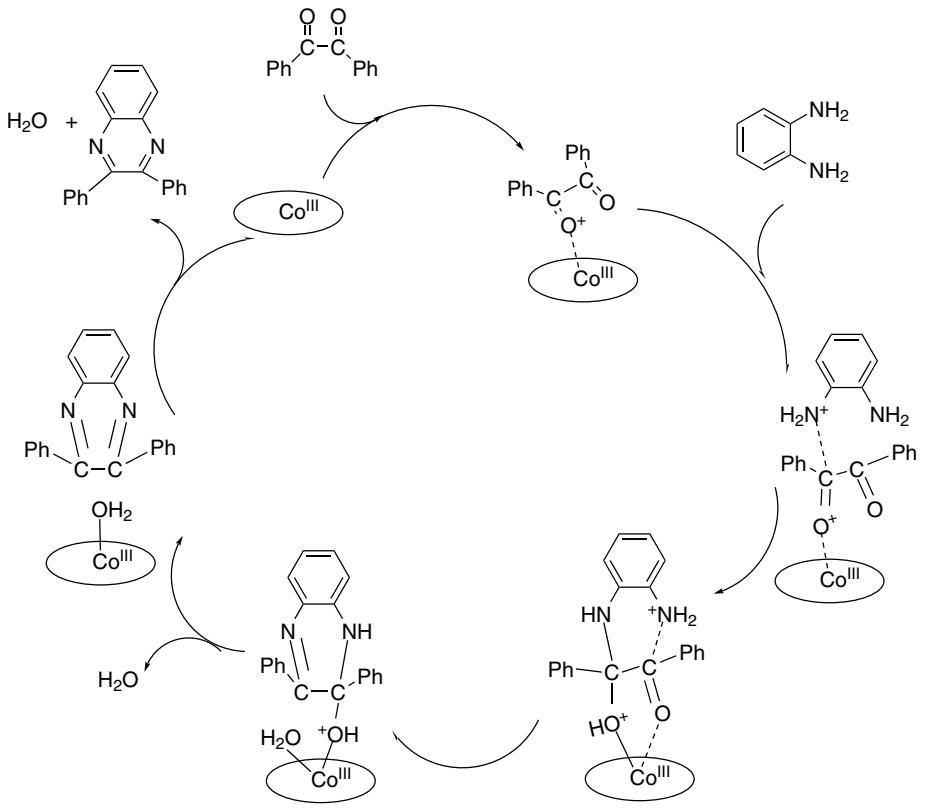
Entry	Diamine	Product	Time (min)	Yield (%)	mp [lit.][ref]
1			10	81	233-235
2			10	80	229-230 [230-232][19]
3			10	78	303-305 [304-306][19]
4			60	50[a] 65[b]	318-320 [319-320][19]
5			15	82	86-88 [81][26]
6			20	78	128-130 [124][27]
7			60	41[a] 63[b]	208-210
8			30	80	129-130 [130-131][19]

(*Continued*)

Table 4. (*Continued*)

Entry	Diamine	Product	Time (min)	Yield (%)	mp [lit.][ref]
9			25	81	115-117 [117-118][25]
10			40	78	175-177 [172][18]
11			60	46[a] 60[b]	193-194 [193-194][25]
12			60	43[a] 59[b]	148-150 [148-150][19]
13			60	45[a] 62[b]	128-130 [125-127][25]
14			60	41[a] 57[b]	118-120
15			60	75	166-167
16			120	72	157-159 [158][18]
17			25	78	180-183

[a] at room temperature, [b] at reflux conditions.



Scheme 2. A proposed mechanism for the condensation of benzene-1,2-diamine with benzil in the presence of Co^{+3} porphyrin

some α-diketones. The results are summarized in Table 4. As it is shown in Table 4, when aryl 1,2-diamines were applied, all of the reactions proceeded efficiently and the desired quinoxalines were obtained in excellent yields and short reaction times. However, alkyl 1,2-diamines afforded the corresponding quinoxaline derivatives in slightly lower yields and longer reaction times. The quinoxalines obtained from aryl 1,2-diamines are more stable than the product from alkyl 1,2-diamine due to the formation of conjugated system in the product. In addition, the structure of α-diketones did not significantly affect on the results of the reaction.

We proposed a mechanism to explain the catalytic behavior of Co(III) porphyrin for the condensation reaction of 1,2-diamines with 1,2-diketones (Scheme 2).

EXPERIMENTAL

General procedures

All chemicals were purchased from Merck or Fluka chemical companies. All known compounds were identified by comparison of their melting points, ^{1}H NMR and ^{13}C NMR data with the authentic samples.

Preparation of porphyrins and metalloporphyrins

Porphyrins were prepared according to reported methods [28–31]. Metalloporphyrins were obtained by standard method [32].

Preparation of quinoxalines from 1,2-diamines and α-diketones

To a mixture of α-diketone (1.1 mmol), metalloporphyrin (0.1 mmol) and EtOH/H_2O (1/3 (v/v), 4 mL) in a 50 mL round-bottomed flask was added 1,2-diamine (1.1 mmol), and the resulting mixture was stirred at room temperature for the times reported in Table 4. After the completion of the reaction, H_2O (10 mL) was added and filtered. The product was dissolved in hot ethanol and recrystallized to obtain the pure product. After the evaporation of the solvent, the catalyst was washed with diethyl ether (5 mL) and reused for another time without the loss of the reactivity.

Selected spectral data

Acenaphtho[1,2-b]quinoxaline. White solid; mp 233–235 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 7.80–7.83 (dd, J_{13} = 1.75, J_{12} = 3.25, 2H, arom), 7.88–7.92 (t, J = 7.5, 2H, arom), 8.15–8.18 (d, J = 4.25, 2H, arom), 8.26–8.29 (dd, J_{13} = 1.75, J_{12} = 3.25, 2H, arom), 8.48–8.50 (d, J = 3.25, 2H, arom). ^{13}C NMR ($CDCl_3$): δ, ppm 122.3, 129.1, 129.6, 129.9, 130.0, 130.4, 132.3, 136.9, 141.7, 154.5. Elemental anal. for $C_{18}H_{10}N_2$: calcd. (found): C, 85.02 (85.11); H, 3.96 (3.92); N, 11.02 (11.08).

8,9-dihydroacenaphtho[1,2-b]pirazine. White solid; mp 166–167 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 2.05 (s, 4H, CH_2), 7.3–7.78 (t, J = 7.5 Hz, 2H, arom), 7.98–8.0 (d, J = 3.5 Hz, 2H, arom), 8.01–8.04 (d, J = 4.2 Hz, 2H, arom).

Elemental anal. for $C_{14}H_{10}N_2$: calcd. (found): C, 81.53 (81.50); H, 4.89 (4.92); N, 13.58 (13.61).

2-phenylquinoxaline. White solid; mp 86–88 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 7.56–7.63 (m, 3H, arom), 7.78–7.85 (m, 2H, arom), 8.17–8.26 (m, 4H, arom), 9.38 (s, 1H, arom). ^{13}C NMR ($CDCl_3$): δ, ppm 128.0, 129.6, 129.6, 130.0, 130.1, 130.6, 130.7, 137.2, 142.0, 142.8, 143.8, 152.3.

6,7-dimethyl-2-phenylquinoxaline. White solid; mp 128–130 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 2.56 (s, 6H, CH_3), 7.54–7.61 (m, 3H, arom), 7.90 (s, 1H, arom), 7.95 (s, 1H, arom), 8.21–8.22 (d, J = 3.5, 2H, arom), 9.3 (s, 1H, arom). ^{13}C NMR ($CDCl_3$): δ, ppm 20.7, 20.8, 127.8, 128.6, 129.1, 129.5, 130.2, 137.6, 140.5, 141.0 141.2, 141.7, 142.8, 151.4.

6-nitro-2,3-diphenylquinoxaline. White solid; mp 193–194 °C. IR (KBr): ν_{max}, cm^{-1} 1520, 1330, 760, 690. ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 7.40–7.44 (t, J = 7.0, 4H, arom), 7.46–7.49 (t, J = 7.0, 2H, arom), 7.59–7.62 (m, 4H, arom), 8.33–8.36 (d, J = 4.7 Hz, 4H, arom), 8.56–8.59 (dd, J_{13} = 1.25, J_{12} = 4.75, 1H, arom), 9.12–9.13 (d, J = 1.2, 1H, arom).

6-methyl-2,3-bis(4-bromophenyl)quinoxaline. White solid; mp 180–183 °C. IR (KBr): ν_{max}, cm^{-1} 1040, 1005, 820. ^{1}H NMR ($CDCl_3$): δ, ppm 2.67 (s, 3H, CH_3), 7.43–7.44 (d, J = 3.75, 4H, arom), 7.53–7.54 (d, J = 3.75, 4H, arom), 7.66–7.67 (d, J = 4.25, 1H, arom), 7.97 (s, 1H, arom), 8.07–8.09 (d, J = 4, 1H, arom). Elemental anal. for $C_{21}H_{14}Br_2N_2$: calcd. (found): C, 55.54 (55.56); H, 3.11 (3.08); Br, 35.19 (35.21); N, 6.17 (6.13).

6,7-dimethyl-2,3-bis(4-methoxyphenyl)quinoxaline. Orange solid; mp 118–120 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 2.54 (s, 6H, CH_3), 3.86 (s, 6H, OCH_3), 6.89 (d, J = 8.7, 4H, arom), 7.50 (d, J = 8.7, 4H, arom), 7.93 (s, 2H, arom). FTIR: ν, cm^{-1} 2800–3000 (ν_{C-H}), 1605 ($\nu_{C=N}$), 1510 (ν_{C-O}), 1240 ($\nu_{C=C}$). Elemental anal. for $C_{24}H_{22}N_2O_2$: calcd. (found): C, 77.81 (77.84); H, 5.99 (5.96); N, 7.56 (7.64).

6-nitro-2-phenylquinoxaline. White-yellow solid; mp 208–210 °C. ^{1}H NMR ($CDCl_3$): δ, ppm 7.64–7.67 (m, 3H, arom), 8.30–8.34 (m, 3H, arom), 8.59 (dd, J_{12} = 9.2, J_{13} = 2.4, 1H, arom), 9.06 (d, J = 2.4, 1H, arom), 9.54 (s, 1H, olefin). FTIR: ν, cm^{-1} 3000–3100 (ν_{C-H}), 1520–1560 ($\nu_{C=N}$, $\nu_{C=C}$), 1340 (ν_{N-O}). Elemental anal. for $C_{14}H_{19}N_3O_2$: calcd. (found): C, 66.93 (66.84); H, 3.61 (3.67); N, 16.73 (16.59).

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Supporting information

Selected spectral data for some tetraarylporphyrins are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

REFERENCES

1. Song LC, Wang LX, Tang MY, Li CG, Song HB and Hu QM. *Organometallics* 2009; **28**: 3834–3841.
2. Reboucas JS, Spasojevic I, Tjahjono DH, Richaud A, Mendez F, Benov L and Batinic-Haberle I. *Dalton Trans*. 2008; **9**: 1233–1242.
3. Moghadam M, Mohammadpoor-Baltork I, Tangestaninejad S, Mirkhani V, Kargar H and Zeini-Isfahani N. *Polyhedron* 2009; **28**: 3816–3822.
4. Che CM and Huang JS. *Chem. Commun*. 2009; **27**: 3996–4015.
5. Gao GY, Jones JE, Vyas JR, Harden D and Zhang XP. *J. Org. Chem.* 2006; **71**: 6655–6658.
6. Mirkhani V, Moghadam M, Tangestaninejad S, Mohammdpoor-Baltork I, Kargar H and Araghi M. *Appl. Catal. A* 2009; **353**: 61–67.
7. Xekoukoulotakis NP, Hadjiantonious MCP and Maroulis AJ. *Tetrahedron Lett*. 2001; **41**: 10299.
8. Noyori R and Takaya H. *Acc. Chem. Res*. 1990; **23**: 345.
9. Leung TW and Dombex BD. *J. Am. Chem. Soc. Commun*. 1992; 205.
10. Firouzabadi H, Sardarian AR, Khayat Z, Karimi B and Tangestaninejad S. *Synth. Commun.* 1997; **27**: 2709.
11. Moghadam M, Tangestaninejad S, Mirkhani V, Mohammadpoor-Baltork I. and Taghavi A. *Catal. Commun*. 2007; **8**: 2087–2095.
12. Seitz LE, Suling WJ and Reynolds RC. *J. Med. Chem*. 2002; **45**: 5604.
13. Badran MM, Botros S, El-Gendy AA, Abdou NA, El-Assi H and Salem A. *Bull. Pharm. Sci*. 2001; **24**: 135.
14. Makinde AY, Luo-Owen X, Rizvi A, Crapo JD, Pearlstein RD, Slater JM and Gridley DS. *Anticancer Res*. 2009; **29**: 107–118.
15. Sakurai T, Shi K, Sato H, Tashiro K, Osuka A, Saeki A, Seki S, Tagawa S, Sasaki S, Masunaga H, Osaka K, Takata M and Aida T. *J. Am. Chem. Soc.* 2008; **130**: 13812–13813.
16. Obata M, Matsuura N, Mitsuo K, Nagai H, Asai K, Harada M, Hirohara S, Tanihara M and Yano S. *J. Polym. Sci., Part A: Polym. Chem.* 2010; **48**: 663–670.
17. Hasaninejad A, Zare A, Mohammadizadeh MR and Karami Z. *J. Iran. Chem. Soc.* 2009; **6**: 153–158.
18. Darabi HR, Mohandessi S, Aghapoor K and Mohsenzadeh F. *Catal. Commun.* 2007; **8**: 389–392.
19. Hasaninejad A, Zare A, Mohammadizadeh MR and Shekouhy M. *Arkivoc* 2008; **13**: 28–35.
20. Srinivas C Kumar CNSSP, Rao VJ and Palaniappan S. *J. Mol. Catal. A: Chem.* 2007; **265**: 227–230.
21. Bhosale RS, Sarda SR, Ardhapure SS, Jadhav WN, Bhusareb SR and Pawar RP. *Tetrahedron Lett*. 2005; **46**: 7183–7186.

22. Bailly C, Echepare S, Gago F and Waring M. *J. Anticancer Drug Des.* 1999; **14**: 291–303.
23. Antoniottia S and Dunach E. *Tetrahedron Lett.* 2002; **43**: 3971–3973.
24. Dailey S, Feast JW, Peace RJ, Sage IC, Till S and Wood EL. *J. Mater. Chem.* 2001; **11**: 2238.
25. Heravi MM, Bakhtiari K, Tehrani MH, Javadi NM and Oskooei HA. *Arkivoc* 2006; **16**: 16.
26. Raw SA, Wilfred CD and Taylor JK. *Org. Biomol. Chem.* 2004; **2**: 788–796.
27. Gazit A, App H, McMahon G, Chen J, Levitzki A and Bohmer FD. *J. Med. Chem.* 1996; **39**: 2170.
28. Johnstone RAW, Nunes ML, Pereira MM, Gonsalves AM and Serra AC. *Heterocycles* 1996; **43**: 1423–1437.
29. Kruper WJ, Chamberlin TA and Kochanny M. *J. Org. Chem*. 1989; **54**: 2753.
30. Jia Z, Deng H and Pu M. *Nucl. Med. Biol*. 2007; **34**: 643–649.
31. Skrzypek D, Madejska I and Habdas J. *Solid State Sci*. 2007; **9**: 295–302.
32. Alder AD, Long FR, Kampas F and Kim J. *J. Inorg. Nucl. Chem*. 1970; **32**: 2443.