Synthesis and evaluation of 2-phenylamino-1,4-naphthoquinones derivatives as potential hypoglycaemic agents

R. Razaque a, A. R. Raza a, M. Irshad b, S. L. Rubab a, S. Batool a, B. Nisar a, Z. Akram c, M. T. Akhtar a, R. Qadir a, Abu Bakar Siddique a, Farzana Siddique a, and M. Saadia h

a University of Sargodha, Institute of Chemistry, Sargodha, Pakistan
b University of Education Lahore, Department of Chemistry, Division of Science and Technology, Lahore, Pakistan
c University of Education, Department of Chemistry, Jauharabad Campus, Jauharabad, Pakistan
d University of Sargodha, Department of Zoology, Sargodha, Pakistan
e University of Lahore, Department of Chemistry, Sargodha Campus, Sargodha, Pakistan
f Griffith University, Health Institute Queensland, School of Medical Sciences, Gold Cost Campus, Queensland, Australia
g Institute of Food Science and Nutrition, University of Sargodha, Sargodha, Pakistan
h Ghazi University, Department of Chemistry, Dera Ghazi Khan, Pakistan

Abstract

Due to the severe side effects revealed by most of the currently used antidiabetic medicines, search for finding new and safe drugs to manage diabetes is continued. Naphthoquinones possessing strong antioxidant properties have been employed as candidates for diabetes therapy. Present study is aimed at finding the antioxidant and hypoglycaemic potential of some novel derivatives of 2-phenylamino-1,4-naphthoquinones (PAN) including chloro, nitro, methyl and bromo (5a-d) derivatives synthesized by single pot experiment. Product crystals were purified by TLC and characterized by FT-IR. The antioxidant potential of the compounds was assayed through DPPH radical scavenging and reducing power activities noted as UV-vis. absorbance. The DPPH assay has showed the powerful antioxidant activity of nitro and bromo derivatives, while the nitro derivative showed the significant reduction potential towards FRAP assay. Hypoglycaemic potential of the compounds was studied in rat animal model. All synthesized compounds revealed better hypoglycaemic activity; however, the chloro-derivative exhibited the more potent hypoglycaemic activity showing about 43% reduction in the mean blood glucose levels of the treated animals. As the bioreduction of naphthoquinones may be influenced by changing its redox properties, it has been noticed that the e-donating resonance effect (+R) of ‘chloro’ group has shown the significant effects on biological activity through stabalization of its imine form which limits the potential of generation of free radicals during bioreduction of quinones and thus has been proposed as the reason of its hypoglycaemic activity. Future studies employing the properties of e-donating groups of PAN may optimize the drug-receptor interaction for better drug designing and drug development strategies against diabetes and also for the clinical trials.

Keywords: diabetes, naphthoquinone derivatives, 2-phenylamino-1,4-naphthoquinones, hypoglycaemic agents, antioxidants.

Resumo

Em razão dos graves efeitos colaterais causados pela maioria dos medicamentos antidiabéticos atualmente utilizados, continua a busca por novos medicamentos seguros para o controle do diabetes. As naftoquinonas, que possuem fortes propriedades antioxidantes, têm sido empregadas como candidatas à terapia do diabetes. O presente estudo visa encontrar o potencial antioxidante e hipoglicemiante de alguns novos derivados de 2-fenilamino-1,4-naftoquinonas (PAN), incluindo derivados de cloro, nitro, metil e bromo (5a-d) sintetizados por experimento em pote único. Os cristais do produto foram purificados por TLC e caracterizados por FT-IR. O potencial antioxidante dos compostos foi testado por meio de atividades de sequestro de radicais DPPH e redução de energia observada como absorção no UV-vis. O ensaio DPPH mostrou a poderosa atividade antioxidante dos derivados nitro e bromo, enquanto o derivado nitro mostrou o potencial de redução significativo para o ensaio FRAP. O potencial hipoglicêmico dos compostos foi estudado em modelo animal de rato. Todos os compostos sintetizados revelaram melhor atividade hipoglicemiante; no entanto, o derivado cloro apresentou atividade hipoglicêmica mais potente, com redução de

*e-mail: msadia@gudgk.edu.pk
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43% nos níveis médios de glicose no sangue dos animais tratados. Como a biorredução de naftoquinonas pode ser influenciada pela alteração de suas propriedades redox, notou-se que o efeito da doação eletrônica por ressonância (+R) do grupo “cloro” tem sido significativo na atividade biológica por meio da estabilização de sua forma imina, que limita o potencial de geração de radicais livres durante a biorredução de quinonas, e, portanto, tem sido proposto como a razão de sua atividade hipoglicemiante. Estudos futuros empregando as propriedades de grupos de doação eletrônica de PAN podem otimizar a interação droga-receptor para melhor planejamento de medicamentos e estratégias de desenvolvimento de medicamentos contra o diabetes e também para os ensaios clínicos.

Palavras-chave: diabetes, derivados da naftoquinona, 2-fenilamino-1,4-naftoquinonas, hipoglicemiantes, antioxidantes.

1. Introduction

Diabetes and its complications increase alarmingly in the world population. Most of the complications arise generally due to the uncontrolled hyperglycaemia and disturbances in rapid catabolism of lipids and protein (Pandhare et al., 2010). Oxidative stress has been considered the main cause of elevated levels of mitochondrial reactive oxygen species (ROS); mostly the superoxide anions aggravate diabetes and its complications. The natural naphthoquinones and their synthetic derivatives have been of interest to treat diseases with key redox properties of the quinone moiety present. The naphthoquinones have shown strong antioxidant activity (Wang et al., 2015; Tabrizi and Chiniforoshan, 2017), antibacterial and antifungal activities (Sanchez-Calvo et al., 2016), and recently evaluated as metabolic enzyme inhibitors (Riaz et al., 2021) as prototypes of new antineoplastic drugs (Guimaraes et al., 2021), and also as emerging agents in combating multidrug-resistant (MDR) pathogens (Mone et al., 2021).

The naphthoquinone scaffolds have been studied as potent anti-diabetic agents and the inhibitors of protein tyrosine phosphatases such as CDC25B (Brun et al., 2005). The amino derivatives of naphthoquinone (Amino-naphthoquinones) are produced naturally in some plants for example, the plant family Caryophyllales (Lopez et al., 2011). These compounds have exhibited various cytotoxic activities and it has been shown that incorporation of amino groups into 1,4-naphthoquinone structures often results in an increase in their antibacterial (Andrade-Guel et al., 2011), antiparasitic (Sharma et al., 2013; Ibis et al., 2014), and antiproliferative activities (Suja et al., 2016). Further, the transition metal complexes of amino-1,4-naphthoquinone ligands have shown the promising biological activity comparable to that of parent free ligand against some bacterial and fungal species (Hassan et al., 2020).

The earlier studies have demonstrated the promising hypoglycaemic activity of thymoquinone (Al-Sa’aidi et al., 2014; Sangi et al., 2015; Bashandy et al., 2015; Saheb et al., 2016) and the rear of the present study was to synthesize some amino-naphthoquinone derivatives with structural similarity to thymoquinone, a well characterized component of essential oil of Nigella sativa with promising activity against diabetes (Gray et al., 2016), and to test for their comparable hypoglycaemic potential (structure-activity relationship study). The synthesized amino-naphthoquinone derivatives also showed some structural similarities to commonly used hypoglycaemic agents for example, sulfonylureas (e.g., tolbutamide 1a) and thiazolindiones (e.g., troglitazone). However, such drugs also have revealed severe side effects and often prescribed only for specific diabetic condition. We assume that our synthesized compounds if trialed clinically, shall show better therapeutic efficiency with very limited side-effects due to structure resemblance with the natural antidiabetic compound, the thymoquinone 2.

It would be of interest to evaluate the synthetic derivatives of amino-naphthoquinone with various substitutions for their hypoglycaemic activity as it has been established that different substituents accounts for different antidiabetic behaviour. Considering the hydrophobicity and electronic factor, the addition of amino functionality (a good nucleophilic agent for chelation or stronger hydrophilic interactions) and/or halogen group to lead compound is quite easy and is according to the Topliss scheme (Patrick, 2002). However, the halogenated drugs have also shown the undesirable response of drug accumulation in lipid tissues. Thus, the nature of the halogen and the point of attachment to the lead, both matter for the chemical reactivity. For example, the replacement of the methyl (R1-group) substituent by chlorine transform the antidiabetic drug ‘tolbutamide 1a into another one ‘chlorpropamide’ 1b with the significant longer half-life (Thomas, 2007).

Keeping in view the importance of halogen groups at ring structure and the limitations of antidiabetic drugs, we synthesized the two of the four amino-naphthoquinone derivatives by incorporating the halogen atoms (Cl and Br) to amino-naphthoquinone skeleton. The experiment shall lead the bases for designing the substituent(s) for amino-naphthoquinones to develop more efficient antidiabetic drugs.

2. Materials and Methods

The chemicals utilized during study were purchased from sigma Aldrich/ Merck. The solvents used in reaction were of analytical grade and used as such.

2.1. Chemical part

Synthesis of 2-(phenylamino)-1,4-naphthoquinones (PAN) 5a-d: The substrate 1,4-naphthoquinone 3 (0.5 g. 3.2 mmol, 2 eq) and p-substituted anilines 4a-d (1.6 mmol, 1 eq) were dissolved in MeOH (50 ml) and stirred at 200 rpm for variable reaction duration followed by reflux at 70 °C. The resultant mixture was cooled to ambient, filtered and the title compounds were crystallized upon standing overnight (Table 1).

The thin-layer chromatography (TLC) was carried out on pre-coated silica gel (0.25 mm, 70-230 mesh) on Al-back
Table 1. The experimental and physical parameters involved in the synthesis and characterization of targeted compounds (5a-d).

|  | m of 4 (mg) | Stirring (h) | Reflux (h) | m of 5 (mg) | Yield (%) | IR (cm⁻¹) |
|---|---|---|---|---|---|---|
| a | 204 | 43 | 6 | 210 | 74 | 1599, 1705 (C=O), 3197 (N–H) |
| b | 221 | 48 | 10 | 203 | 69 | 1504 (N=O), 1598, 1707 (C=O), 3202 (N–H) |
| c | 171 | 48 | 6 | 208 | 79 | 1602, 1700 (C=O), 3199 (N–H) |
| d | 275 | 45 | 12 | 249 | 76 | 1597, 1705 (C=O), 3198 (N–H) |

The reducing power of the synthesized PAN derivatives 5a-d was determined following a reported method (Benzie and Strain, 1996). The stock solutions of 5a-d were prepared in DMSO and then different dissolutions were prepared (1–200 µM). To each millilitre of different dilutions, 2.5 ml of 4-(2,4-DNP) propanoic acid was used as standard antioxidant. The absorbance was noted at 700 nm using spectrophotometer. The ascorbic acid was used as standard antioxidant.

2.5. Hypoglycaemic potential of the synthesized PAN derivatives (5a-d)

The ability of synthesized PAN compounds 5a-d to lower the blood glucose levels was analyzed in diabetic albino rats (average weight of 200 g) purchased from University of Veterinary and Animal Sciences, Lahore (UVAS, Pakistan). These were maintained on standard laboratory condition of room temperature, humidity and under 12 h dark–light cycle at the Department of Pharmacy, University of Sargodha, Pakistan. The experiment was conducted following the instructions of animal handling procedures under the principles of laboratory animal care and use guidelines (WHO, 1985). The blood glucose levels were determined using glucometer (On Call EZ II, ACON® Laboratories, Inc.).

2.6. Statistical analysis

The results are presented as means ± standard error of means. For establishing significant differences between groups, data were analyzed by One-way ANOVA. The values were considered statistically significant at p<0.05 using SPSS (Statistical Package for Social Sciences) software, version 21.0.

3. Results and Discussion

3.1. Chemistry: synthesis of 2-phenylamino-1,4-naphthoquinones (PAN) derivatives

The four PAN derivatives 5a-d were synthesized by single pot synthesis protocol. The 1,4-naphthoquinone 3 was stirred with substituted anilines 4a-d in MeOH at ambient for a variable reaction duration. The resulting products (5a-d) were isolated and purified by crystallization from MeOH (Scheme 1). Contrary to the many other cases, instead of altering the electron density of the phenyl ring of naphthoquinone, to
make it more reactive (Satheshkumar et al., 2014), we have altered the electron densities on PhNH₂ by incorporating the substituents with electron withdrawing or donating effects to facilitate the addition reaction in the presence of MeOH, which is indicated by the high percent yields (Table 1). The synthesized compound would show hybridization of PAN according to the electronic properties of the substituent. It has been reported that the resonance effects dominates the inductive effects when the electron donating substitents are incorporated in the quinone ring. However, in the case of electron withdrawing groups the reverse may be true (Macias-Ruvalcaba et al., 2002).

Following scheme shows the effects of incorporation of e-withdrawing and donating groups to the PAN structure (Scheme 2 adopted from Satheshkumar et al., 2014, and redrawn). The e-withdrawing group causes the delocalization of electron pair of N in phenyl ring, which decreases its basicity. While an e-donating group inhibits the delocalization (due to lone pair-n electron pair repulsions) of electron pair of N in phenyl ring, which increases its basicity. The availability/localization of electron pair on nitrogen is the key parameter in biological action. The general structure of the compound which is to be derivatized showed in Figure 1 whose nomenclature are 1a N-Butyl-N-(4-methylbenzenesulphonyl) carbamide, 1b N-Propyl-N-(4-methylbenzenesulphonyl) carbamide and 2 2-Methyl-5-propylbenzoquinone respectively.

The characterization of synthesized compounds 5a-d by IR revealed enough information to authenticate the formation of targeted compounds. The IR spectrum of naphthoquinone 3 (the substrate) shows only one broad absorbance at 1610 cm⁻¹ for both carbonyls since both C=O are symmetrical but the position of signal in spectrum is quite unexpected (normal range 1690-1720 cm⁻¹). However, the IR spectra of synthesized PAN derivatives 5a-d showed two signals around 1690 and 1600 cm⁻¹ signifying a change due to the induction of PhNH moiety. The larger 𝜈 value (1690 cm⁻¹) is exhibited by the C=O not in conjugation with phenylamino functionality; whereas, the smaller 𝜈 value (1600 cm⁻¹) belongs to the C=O in conjugation with phenylamino moiety (Figure 2). The high energy IR region (3100–4000 cm⁻¹) also confirmed the formation of targeted compounds 5a-d. The substrate 3 showed an intense absorbance of aromatic sp²C–H stretching at 3053 cm⁻¹. The spectra of synthesized compounds 5a-d exhibit an intense absorbance of hydrogen bonded N–H stretching 3200±5 cm⁻¹ and a poor absorbance of aromatic sp²C–H cm⁻¹ at 3000±3 cm⁻¹ (Figure 3). The appearance of intense absorbance has provided the clear indication of an amino functionality, which may exist in other tautomeric (imine) form as well (Scheme 3).

The proposed mechanism is displayed in Scheme 4. Two equivalents of 1,4-naphthoquinone 3 and one equivalent of p-substituted amines 5a-d were used since 3 acts as not only substrate but also as an oxidizing agent. The conjugate addition of amines 4a-d to...
1,4-naphthoquinone 3 followed by deprotonation results in the formation of quinone 6 that may tautomerize to 7 or 8. The oxidation of 8 by 3 following single electron transfer (SET) furnishes the formation of a radical cation 10 that converts to resonance stabilized free radical 11. Another course of SET to 11 results in the formation of targeted compounds 5a-d, which may also exist in its other tautomeric form 15 (Scheme 4).

3.2. Biology: antioxidant and hypoglycaemic potential

The knowledge about the chemical structure of a natural antioxidant (phytochemical) provides bases for synthesis of more specific chemical compounds with enhanced bioactivity. Therefore, many researchers have synthesized a variety of chemical compounds and evaluated their antioxidant potential. The nitrogen containing heterocyclic compounds as oxindoles were synthesized and studied for their antioxidant potential with respect to ascorbic acid. It was inferred that the structural variations bring about change in bioactivity e.g., if halogens (Cl or Br) were substituted in the aromatic ring, it sharply enhanced the antioxidant potency of the compound (Hossain et al., 2009). The radical scavenging activity of naphthoquinones has also been studied and it was found that the antioxidant potential of 2-aminothiophene compounds has increased by introducing the naphthoquinones moiety to the compounds (Gouda et al., 2013). In the present study, among four PAN derivatives tested, the nitro and bromo derivatives have shown the better radical scavenging activity as compared to the chloro derivative, however, the methyl derivative has shown no activity at all. The bromo derivative was found with the maximum antioxidant activity as exhibited by the higher %RSA (Figure 4). Fourteen different concentrations (1–200 µM) of compounds 5a–d were prepared and the highest scavenging activity was noted for 5b at 135 µM concentration and also a significant activity was noticed for 5d at 120 µM concentration. Since the maximum %RSA was exhibited by the Br-derivative, hence, the current results further support the earlier findings (Hossain et al., 2009), and also explain the importance of electron donating groups on the PAN structure for their radical scavenging activity.

The Fe³⁺ reducing power (FRAP) assay was also conducted to evaluate the reduction potential of synthesized compounds (5a–d). The assay results have been presented in Table 3.

We find that 5c has shown more activity towards Fe³⁺ reduction (except at 30 µM) indicating the higher antioxidant potential after ascorbic acid. Here, the nitro group with greater electron withdrawing effect showed the more significant reduction potential among PAN derivatives. While evaluating 5a–d for their potential against diabetes induced hyperglycemia, all compounds showed significant reduction in mean blood glucose levels of the...
experimental rats. However, the 5a (chloro-derivative of PAN) showed the most significant (p<0.05) activity against hyperglycemia in rats bringing about 43% reduction in the mean blood glucose levels; near the control value (Figure 5).

The search of finding the most potent and safe antidiabetic agent provoked different researchers to tune their efforts for synthesis of compounds structurally related to some natural antidiabetics. Konatham et al. (2010) synthesized the curcumin derivatives and reported four derivatives (H, Cl, Me₂N, OH) with promising antidiabetic activities even more than the curcumin. Moreover, similar to our findings, they reported the Me-derivative with inferior antidiabetic activity as compared to curcumin (Konatham et al., 2010). Similarly, Kini and Ghate, 2011) reported the synthesis of 3-[5'-methyl-2'-aryl-3'-(thiazol-2"-yl amino) thiazolidin-4'-one] coumarins and found some of the compounds with Cl and Br-substituents with significant hypoglycaemic activity (Kini and Ghate, 2011).

We also have found the CI-derivative of phenylamino-naphthoquinone (5a) as the most potent antidiabetic agent. Both 5a and 5d shows similar electronic effects (‒I, +R effects). However, we found more hypoglycaemic potential of 5a as compared to 5d; the reason would be the greater size of the Br-group, which might not fill the binding pocket of the receptor. The 5b exhibits more electron withdrawing potential, but having high polarity (π=0.86) than 5a (π=0.71) and large dipole moments. It has been considered as hydroneutral and thus supposed not so hydrophobic to interact with target receptor on cell membrane (Sagawa and Shikata, 2014). The incorporation of Me-groups usually reduces the water solubility and consequently enhances the ability of analogue to absorb into biological membrane but reduces its ability to be released from the biological membranes into aqueous media. It has also been noted that Me-group may develop more suitable interactions with the binding site of the receptor and best fit the pocket on the target site (Patrick, 2002).

### 3.3. Proposed mechanism of action for 5a

It has been reported earlier that in the biological system, the quinone may be reduced to semiquinone (a free radical) and also to hydroquinone by the enzyme cytochrome P450 reductase and other flavoprotein enzymes. These intermediary species are re-oxidized by molecular oxygen (O₂) and generate ROS, such as superoxide, OH and H₂O₂ (Kumagai et al., 2012). Bio-reduction of
naphthoquinones may be influenced by changing the redox properties of naphthoquinones. It has been found that presence of electron-rich substituents at the quinone moiety lowers its reduction potential, thus they become more reactive. However, for the mechanism of action of 5a, we propose that the incorporation of amine moiety to the quinone structure limit the free radical generating ability of the quinones and also further addition of any chemical group having electron donating resonance effect may stabilize the imine form of the compound (Figure 6). By utilizing the oxidation-reduction properties of its quinone moiety, naphthoquinones may act as generators of free radicals as their semiquinone radicals may lead to the formation of reactive oxygen species. This induces the cytotoxicity. Mainly the cytotoxic properties of naphthoquinones have been reported to be highly dependent on their chemical properties (Monks et al., 1992). However, the incorporation of e-donating group at para position of 2-phenylamino-1,4-naphthoquinone (PAN) has induced the favourable change in biological properties of PAN conferring more cyto-protective properties to it.

4. Conclusions

The compounds 2-phenylamino-1,4-naphthoquinones (PAN) have been the subject of interest for their diverse use in medical and biological applications as naphthoquinone amino derivatives exhibit interesting redox properties which make these potential targets of medicine. Mostly the synthetic naphthoquinone(s) have shown antimicrobial activities however; very less data is available regarding its potential against diabetes.

In present study the four synthesized PAN derivatives were tested for its antioxidant potential and hypoglycaemic activity in vivo to stimulate research utilizing the medicinal benefits of PAN derivatives in drug discovery and development. All the synthesized compounds showed better antioxidant and hypoglycaemic activity, however, the chloro derivative exhibited the more potent hypoglycaemic activity may be due to the presence of e-donating resonance effect (+R) of chloro group. It is inferred that the addition of chloro group to the PAN structure provide stability to its imine form which limits the potential of generation of free radicals of quinones during bio-reduction, which may be proposed as reason for the potential hypoglycaemic activity exhibited by PAN chloro derivative. The present study findings need additional efforts to optimize drug-receptor interactions for better drug designing strategies and to develop more potent antidiabetic derivatives containing the 2-phenylamino-1,4-naphthoquinones moieties. The study will stimulate the need for further clinical trials of the synthesized compounds as drug(s) based on naphthoquinone derivatives for therapy against diabetes.

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References

Al-Saaidi, J.A., Kareem, H.M. and Al-Tameemi, W.T., 2014. Antihyperglycaemic effects of thymoquinone in diabetic rats. Basrah Journal of Veterinary Research, vol. 13, no. 2, pp. 180-192. http://dx.doi.org/10.33762/bvret.2014.98809.

Andrade-Guel, M.L., López-López, L.I. and Sáenz-Galindo, A., 2011. Estudiosin tético y caracterización por infrareda de derivados 2-(amino)-1,4-naftoquinona y su evaluación antibacteriana preliminar. TIP Revista Especializada en Ciencias Químico-Biológicas, vol. 14, no. 2, pp. 75-82.

Bashandy, S., Jaleel, G., Abdallah, H. and Harraz, S., 2015. Therapeutic implications of thymoquinone in the management of diabetes mellitus and its complications. American Journal of Phytomedicine and Clinical Therapeutics, vol. 3, no. 3, pp. 287-301.

Benzie, I.F. and Strain, J.J., 1996. The ferric reducing ability of plasma (FRAP) as a measure of “antioxidant power”: the FRAP assay. Analytical Biochemistry, vol. 239, no. 1, pp. 70-76. http://dx.doi.org/10.1006/abio.1996.0292. PMID:8660627.

Brun, M.P., Braud, E., Angotti, D., Mondésert, O., Quarantra, M., Montes, M., Miteva, M., Gresh, N., Duccimmun, B. and Garbay, C., 2003. Design, synthesis, and biological evaluation of novel naphthoquinone derivatives with CDC25 phosphatase inhibitory activity. Bioorganic & Medicinal Chemistry, vol. 11, no. 16, pp. 4871-4879. http://dx.doi.org/10.1016/j.bmc.2005.05.005. PMID:15921913.

Gouda, M.A., Eldien, H.F., Girges, M.M. and Berghot, M.A., 2013. Synthesis and antioxidant activity of novel series of naphthoquinone derivatives attached to benzothiophene moiety. Medicinal Chemistry, vol. 3, no. 2, pp. 2228-2232.

Gray, J.P., Burgos, D.Z., Yuan, T., Seeram, N., Rebar, R., Follmer, R. and Heart, E.A., 2016. Thymoquinone, a bioactive component of Nigella sativa, normalizes insulin secretion from pancreatic β-cells under glucose overload via regulation of malony-CoA. American Journal of Physiology, Endocrinology and Metabolism, vol. 310, no. 6, pp. E394-E404. http://dx.doi.org/10.1152/ajpendo.00250.2015. PMID:26786775.

Guimaraes, D.G., Consalves, A.A., Rolim, L.A., Araujo, E.C., Santos, V.L.A., Silva, M.F.S., Oliveira, F.C.E., Costa, M.P., Pessoa, C., Coulart, M.O.F., Silva, T.L., Santos, D.C. and Araujo, C.R.M., 2021. Naphthoquinone-based hydrazine hybrids: synthesis and potent activity against cancer cell lines. Medicinal Chemistry, vol. 17, no. 9, pp. 945-955. http://dx.doi.org/10.2174/1573406416666201817164308. PMID:32807066.

Hassan, F., Faye, M. and Abdalla, N., 2020. Coordination behavior and biological activity of some transition metal complexes with 2-acetyl and 2-formyl-3-amino-1,4-naphthoquinone ligands. Open Journal of Inorganic Non-metallic Materials, vol. 10, no. 02, pp. 15-29. http://dx.doi.org/10.4236/ojinnm.2020.102002.

Hossain, M.M., Shaah, S.K. and Aziz, F., 2009. Antioxidant potential study of some synthesized N-heterocycles. Bangladesh Medical Journal, vol. 38, no. 3, pp. 151-156. http://dx.doi.org/10.3329/bmj.v38i3.3567.

Hussain, A.I., Anwar, N. and Nasir, A., 2012. Naphthoquinones: potential targets for cancer therapy. Asian Journal of Chemistry, vol. 24, no. 10, pp. 5545-5557. http://dx.doi.org/10.3923/ajc.2012.5545.5557.

Hussain, A.I., Anwar, N. and Nasir, A., 2012. Naphthoquinones: potential targets for cancer therapy. Asian Journal of Chemistry, vol. 24, no. 10, pp. 5545-5557. http://dx.doi.org/10.3923/ajc.2012.5545.5557.

Khan, A., Morshed, B., Ghafoor, S., Zin, M. and Islam, M.H., 2013. Synthesis, spectroscopic and biological evaluation of naphthoquinone derivatives. Bangladesh Journal of Pharmaceutical Sciences, vol. 10, no. 2, pp. 227-232. http://dx.doi.org/10.3329/bbps.v10i2.17307.

Khan, A., Morshed, B., Ghafoor, S., Zin, M. and Islam, M.H., 2013. Synthesis, spectroscopic and biological evaluation of naphthoquinone derivatives. Bangladesh Journal of Pharmaceutical Sciences, vol. 10, no. 2, pp. 227-232. http://dx.doi.org/10.3329/bbps.v10i2.17307.
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Research Council Bulletin, vol. 35, no. 2, pp. 49-52. http://dx.doi.org/10.3329/bmbcr.v35i2.2564. PMid:20120779.

IBIS, C., TUYUN, A.F., BAHAR, H., AYLA, S.S., STASEVYCH, M.V., MUSYANOVYCH, R.Y., KOMAROVSKA-POROKHNYAVETS, O. and NOVIKOV, V., 2014. Nucleophilic substitution reactions of 1,4-naphthoquinone and biologic properties of novel S-, S-, N-, and S-substituted, 1,4-naphthoquinone derivatives. Medicinal Chemistry Research, vol. 23, no. 4, pp. 2140-2149. http://dx.doi.org/10.1007/s00044-013-0806-y.

KINI, D. and GHATE, M., 2011. Synthesis and oral hypoglycaemic activity of 3-[5′-Methyl-2′-aryl-3′-(thiazol-2′-yl amino) thiazolidin-4′-one] coumarin derivatives. E-Journal of Chemistry. vol. 8, no. 1, pp. 386-390. http://dx.doi.org/10.1155/2011/258670.

KONATHAM, S., KUMAR, P. and AIKUNURUL, J., 2010. Synthesis and screening of anti diabetic activity of some novel curcumin curcumol analogues. International Journal of Pharma and Bio Sciences, vol. 1, no. 2, pp. 1-12.

KUMAGAI, Y., SHINKAI, Y., MIURA, T. and CHO, A.K., 2012. The chemical biology of naphthoquinones and its environmental implications. Annual Review of Pharmacology and Toxicology, vol. 52, no. 1, pp. 221-247. http://dx.doi.org/10.1146/annurev-pharmtox-010611-134517. PMid:21942631.

LOPEZ, L.I., LEYVA, E. and GARCIA, R., 2011. Naphthoquinones: more than natural pigments. Revista Mexicana de Ciencias Farmaceuticas, vol. 42, no. 1, pp. 6-17.

MACÍAS-RUVALCABA, N., CUEVAS, G., GONZÁLEZ, I. and AGUILAR-MARTÍNEZ, M., 2002. Relationship between molecular structure and electron targets in the electroreduction of benzo[c]carbazole-derivatives and anilinonaphthoquinones. Experimental and theoretical study. The Journal of Organic Chemistry, vol. 67, no. 11, pp. 3673-3681. http://dx.doi.org/10.1021/jo01083k. PMid:12076797.

MARTINS, F.T., DORIGUETTO, A.C., SOUZA, T.C., SOUZA, K.R., SANTOS, M.H., MOREIRA, M.E. and BARBOSA, L.C., 2008. Composition, and anti-inflammatory and antioxidant activities of the volatile oil from the fruit peel of Garcinia cambogia. Chemistry & Biodiversity, vol. 5, no. 2, pp. 251-258. http://dx.doi.org/10.1002/cbdv.200890022. PMid:18293438.

MONE, N.S., BHAGWAT, S.A., SHARMA, D., CHASKAR, M., PATIL, R.H., ZAMBONI, P., NAWANI, N.N. and SATPUTE, S.K., 2021. Naphthoquinones and their derivatives: emerging trends in combating microbial pathogens. Coatings, vol. 11, no. 4, pp. 434. http://dx.doi.org/10.3390/coatings11040434.

MONKS, T.J., HANZLIK, R.P., COHEN, G.M., ROSS, D. and GRAHAM, D.G., 1992. Quinone chemistry and toxicity. Toxicology and Applied Pharmacology, vol. 112, no. 1, pp. 2-16. http://dx.doi.org/10.1016/0041-008X(92)90273-U. PMid:1733045.

PANDEHARE, R.B., SANGAMESWARAN, B., MOHITE, P.B. and KHANAGE, S.G., 2010. Aqueous extracts of the leaves of Sesbanias punica reduces development of diabetic nephropathy in streptozotocin-induced diabetic rat. Bangladesh Journal of Pharmacology, vol. 5, no. 2, pp. 103-106. http://dx.doi.org/10.3329/bjp.v5i2.7592.

PATRICK, G.L., 2002. An introduction to medicinal chemistry. Oxford: Oxford University Press.

RIAZ, M.T., YAQUB, M., SHAFIQ, Z., ASHRAF, A., KHALID, M., TASLIMI, P., TAS, R., TUZUN, B. and GULCIN, I., 2021. Synthesis, biological activity and docking calculations of bis-naphthoquinone derivatives from Lawsonia. Bioorganic Chemistry, vol. 114, pp. 105069. http://dx.doi.org/10.1016/j.bioorg.2021.105069. PMid:34134033.

SAGAWA, N. and SHIKATA, T., 2014. Are all polar molecules hydrophobic? Hydration numbers of nitro compounds and nitriles in aqueous solution. Physical Chemistry Chemical Physics, vol. 16, no. 26, pp. 12362-12370. http://dx.doi.org/10.1039/C4CP01280A. PMid:24871926.

SAHEB, S.H., DESAI, S.D., KUSAI, K.D. and HASEENA, S., 2016. Antioxidant Effect of nigella sativa seed powder and thymoquinone in normal and streptozotocin induced diabetic albino rats. International Journal of Integrative Medical Sciences, vol. 3, no. 3, pp. 242-247. http://dx.doi.org/10.19095/ijims.2016.108.

SÁNCHEZ-CALVO, J.M., BARBERO, G.R., GUERRERO-VÁSQUEZ, G., DURÁN, A., MACÍAS, M., RODRÍGUEZ-IGLESIAS, M.A. and MOLINILLO, J.M.G. and MACÍAS, F.A., 2016. Synthesis, antibacterial and antifungal activities of naphthoquinone derivatives: A structure–activity relationship study. Medicinal Chemistry Research, vol. 25, no. 6, pp. 1274-1285. http://dx.doi.org/10.1007/s00044-015-1550-x.

SANGI, S.M.A., SULAIMAN, M.I., EL-WAHAB, M.F., AHMEDANI, E.I. and ALLI, S.S., 2015. Antihyperglycemic effect of thymoquinone and oleuropein, on streptozotocin-induced diabetes mellitus in experimental animals. Pharmacognosy Magazine, vol. 11, no. 44, suppl. 2, pp. S251-S257. http://dx.doi.org/10.4103/0973-1296.166017. PMid:26664013.

SATHESHKUMAR, A., GANESH, K. and ELANGO, K.P., 2014. Charge transfer facilitated direct electrophilic substitution in phenylaminonaphthoquinones: experimental, theoretical and electrochemical studies. New Journal of Chemistry, vol. 38, no. 3, pp. 993-1003. http://dx.doi.org/10.1039/c3nj01228j.

SHARMA, U., KATOCH, D., SOOD, S., KUMAR, N., SINGH, B., THAKUR, A. and GULATI, A., 2013. Synthesis, antibacterial and antifungal activity of 2-amino-1,4-naphthoquinones using silica-supported perchloric acid (HClO 4-SiO 2) as a mild, recyclable and highly efficient heterogeneous catalyst. Indian Journal of Chemistry Sect. B, vol. 52B, no. 11, pp. 1431-1440.

SUJA, T.D., DIVYÁ, K.V.L., NAIK, L.V., KUMAR, A.R. and KAMAL, A., 2016. Copper-catalyzed three-component synthesis of aminonaphthoquinone–sulfonylamidine conjugates and in vitro evaluation of their antiproliferative activity. Bioorganic & Medicinal Chemistry Letters, vol. 26, no. 8, pp. 2072-2076. http://dx.doi.org/10.1016/j.bmcl.2016.02.071. PMid:26948541.

TABRIZI, L. and CHINIFOROUSHAN, H., 2017. Designing new iridium (III) arene complexes of naphthoquinone derivatives as anticancer agents: a structure–activity relationship study. Dalton Transactions, vol. 46, no. 7, pp. 2339-2349. http://dx.doi.org/10.1039/C6DT04339A. PMid:28138683.

THOMAS, C.G., 2007. Medicinal chemistry: an introduction. Chichester: John Wiley & Sons.

WANG, S.H., LO, C.Y., GWO, Z.H., LIN, H.J., CHEN, L.G., KOU, C.D. and WU, Y.J., 2015. Synthesis and biological evaluation of lipophilic 1, 4-naphthoquinone derivatives against human cancer cell lines. Molecules, vol. 20, no. 7, pp. 11994-12015. http://dx.doi.org/10.3390/molecules200711994. PMid:26133763.

WORLD HEALTH ORGANIZATION – WHO, 1985. Principles of laboratory animal care. WHO Chronicle, vol. 39, pp. 51-56.