Journal of Biosciences and Medicines, 2023, 11, 105-123
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Relative Molecular Similarity in Compound Structures Modulating Neurodegenerative Apoptosis

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How to cite this paper: Williams, W.R. (2023) Relative Molecular Similarity in Compound Structures Modulating Neurodegenerative Apoptosis. *Journal of Biosciences and Medicines*, **11**, 105-123.
https://doi.org/10.4236/jbm.2023.112008

Received: January 3, 2023
Accepted: February 11, 2023
Published: February 14, 2023

Abstract

Neurodegeneration is attributable to metabolic disturbances in the various cell types responsible for this condition, in respect of glucose utilisation and dysfunctional mitochondrial oxidative mechanisms. The properties of neurotoxins and antagonists that limit their action are well documented in disease models, whereas effective therapy is very limited. Cell apoptosis, a general marker of neurodegeneration, is also of therapeutic interest in the treatment of cancer. cGMP nucleotide influences apoptosis and has a role in maintaining equilibrium within cell redox parameters. The chemical structure of cGMP provides a comparative template for demonstrating relative molecular similarity within the structures of natural and synthetic compounds influencing tumour cell apoptosis. The present study uses computational software to investigate molecular similarity within the structures of cGMP and compounds that modulate cell apoptosis in experimental models of diabetic peripheral neuropathy (DPN), Parkinson's and multiple sclerosis. Differential molecular similarity demonstrated in neurotoxin and antagonist structures implicate metabolite impairment of cGMP signaling function as a common mechanism in the initial phases of these neurodegenerative conditions.

Keywords

Apoptosis, cGMP, Neurodegeneration, Neurotoxins, Molecular Similarity

1. Introduction

Cell apoptosis is a feature of several major pathological conditions, including diabetes, cancer, motor neurone and Parkinson's diseases. Experimental models of neurodegeneration initiated by cytotoxic compounds are useful for developing antagonists of apoptosis, whereas therapeutics in the cancer field exploit

apoptotic properties to reduce tumour cell burden. Glucose initiates oxidative stress and Schwann cell dysfunction in a model of diabetic peripheral neuropathy (DPN) [1]. Glucose, streptozotocin and palmitic acid induced oxidative damage to Schwann cells and pancreatic β-cells responds favourably to the protective effects of drugs with very different chemical structures [1] [2] [3]. Hormones, vitamins and steroid compounds that induce [4] [5] or protect against cell apoptosis [6] [7] contribute additional insight into the molecular mechanisms of neurodegeneration. The oxidative stress generated by cell mitochondria underlies a neurodegenerative etiology that is influenced little by clinical therapy [8].

Demyelinating diseases are characterised by the malfunction of oligodendrocytes and oligodendrogenesis [9]. Steroid hormones modulate demyelination and the apoptotic cell death central to the pathogenesis of multiple sclerosis (MS) [10]. Mitochondrial dysfunction and neuroinflammation feature markedly in the neuron degeneration of MS, Parkinson's and Alzheimer's diseases [8] [11]. The hippocampal neurons of patients with Parkinson's and Alzheimer's demonstrate excessive mitochondrial fragmentation [12]. Reports that identify type-2 diabetes as a risk factor for both diseases may implicate a shared mechanism of glucose dysregulation [13] [14]. Incremental rises in glycaemic variability in individuals are associated with a higher risk of Parkinson's disease [15]. Neurons operate optimally within narrow glucose, oxygen and redox equilibrium parameters, and in cell culture several compounds protect against oxygen-glucose deprivation/reperfusion. The muscarinic agonist xanomeline, for example, protects rat cortical neurons by inhibiting reactive oxygen species (ROS) production and apoptosis; the mechanism is unknown [16].

Previous work has demonstrated that apoptosis-modulating compounds of interest in cancer therapy relate to the structure of the nucleotide cGMP [17]. A high proportion of these compounds both inhibits and initiates tumour cell apoptosis; their chemical structures provide alternative fitting patterns on a cGMP template [18]. Regulatory effects of cGMP and cGMP signaling are not confined to the cell membrane and cytosol, as cGMP impacts opening of the mitochondrial permeability transition pore and mitoK(ATP) channel [19]. The accumulation of cGMP is associated with mitochondrial dysfunction in Leydig cells [20]. Defective ROS producing mitochondria are degraded by the associated proteins PINK1 and PARKIN, resulting in mitophagy; a process impaired in Parkinson's and relevant to neurodegenerative diseases in general [11] [21] [22]. Neural cell survival and dependence on cGMP and cGMP signaling [23] forms the basis for this investigation on relative molecular similarity within the structures of apoptosis modulating compounds of interest in the research and treatment of the above neurodegenerative diseases.

2. Methods

2.1. Compound Structures

The research literature identifies many apoptosis-modulating compounds rele-

vant to neuron degeneration in Parkinson's, motor neurone disease (MND), demyelinating diseases and the peripheral neuropathy of diabetes. Apoptosis and disease-inducing compounds investigated in animal models and cell culture: palmitic acid [3], dexamethasone [5], ceramide [24], glucose [25], tolbutamide [25], MPTP (1-methyl-4phenyl-1,2,3,6-tetrahydropyridine) [26], paraquat [26], rotenone [26], ethidium bromide [27], cuprizone [28], 3-nitro-L-tyrosine [29], streptozotocin [30], pentylenetetrazole (PTZ) [31], metamphetamine [32], lysophosphatidylcholine [33], sphingosine [34]. Compounds providing protection against experimentally induced diabetes and β-cell apoptosis: loganin [1], taurine [2], silibinin [3], 17β-estradiol [6], vitamin D3 [7], mdivi-1 [12], metformin [12], gliclazide [35], nicotinamide [36], telmisartan [37]. Compounds providing protection against apoptosis in animal models of Parkinson's and MS respectively: ursolic acid [26], astilbin [26], β-lapachone [26], papaverine [26], embelin [26], dexrazoxane [26], schisandrin A [26], 20-hydroxyecdysone [38], NE52-QQ57 [39]; magnol [40], cannabidiol [41], monomethylfumarate [42], glucosylceramide [43]. Compounds providing protection against apoptosis and motor neurone degeneration: sphingosine-1-phosphate [24], metformin [31], thymoquinone [44], citicoline [45], nitrovinyl benzoic acid (4-[(1E)-2-nitrovinyl] benzoic acid) [46], ambroxol [47], isofagomine [47], fingolimod [47], fasudil [48], Y-27632 [48], acerogenin [49]. Xanomeline [16], telmisartan [37], orientin [50], geniposide [51], licochalcone A [52], taraxasterol [53], acetylcarnitine [54], atorvastatin [55], riluzole [56] and sulforaphane [57] protect neurons against oxygen-glucose deprivation/reperfusion. 3-nitrotyrosine is an oxidative-stress marker [58]. Compound chemical structures are taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

2.2. Molecular Modeling

The Nemesis software program (Oxford Molecular version 2.1) is used to build molecular structures from contents of the program fragment file and minimise structures by conformational analysis. Compound structures used in fitting are minimum energy conformers in an uncharged form. The conformation of the cGMP template structure is described by the torsion angle C8N9C1'O9-33˚ [18]. The computational program fits paired molecular structures on a three-point basis. Fitting-points, comprised of atoms of similar type and partial charge within compound and nucleotide structures, are identified in the text and **Table 1** with respect to the nucleotide labels. The colour-coded atoms in the figures identify ligand fitting-points: carbon-green, nitrogen-blue, oxygen-red, sulphur-yellow. Bond order within the molecular structures is not shown, to improve on presentation. The Nemesis program computes goodness-of-fit values, in respect of inter-atomic distance at each fitting-point and root mean square (RMS) value.

3. Results

Compound structures with neurotoxic potential, given in **Figure 1**, fit to the

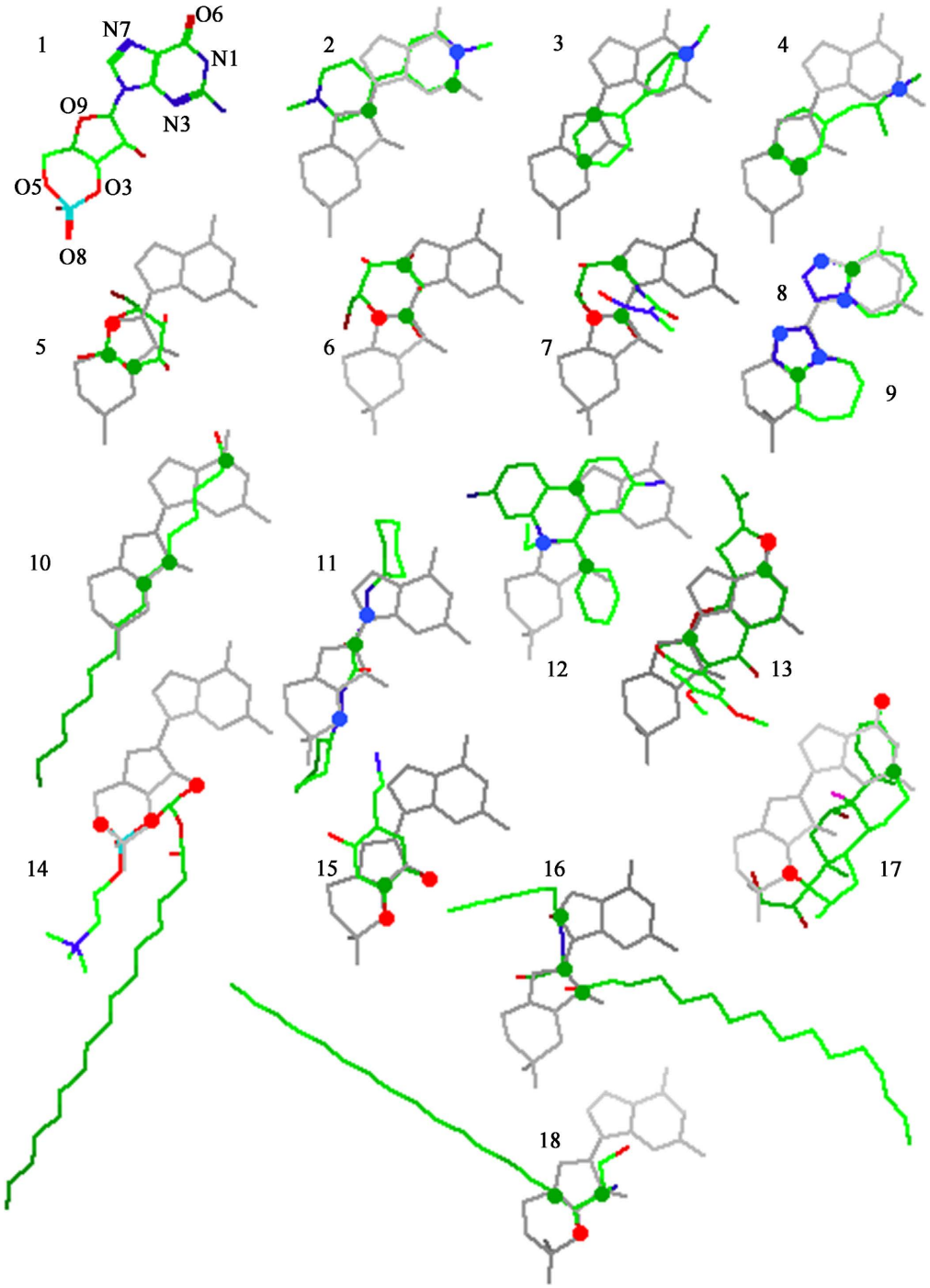
Table 1. Fitting data of compounds with neurotoxic and protective effects in experimental models of Parkinson's, diabetes, neurodegenerative and demyelinating conditions.

compound	Fitting points	Interatomic distance	RMS
3-nitrotyrosine	C3'C2'C8	0.09, 0.10, 0.03	0.0108
6-hydroxydopamine	O3O2'C3'	0.04, 0.02, 0.04	0.0024
17β-estradiol	C4'C2'C2	0.10, 0.09, 0.03	0.0064
20-hydroxyecdysone	N9C1'O8	0.10, 0.08, 0.03	0.0109
acerogenin	C1'C4'O9	0.07, 0.07, 0.09	0.0028
acetylcarnitine	C1'C3'O8	0.10, 0.11, 0.11	0.0251
acetylcarnitine	C1'C3'O3	0.09, 0.07, 0.04	0.0055
ambroxol	C8N9O8	0.02, 0.07, 0.05	0.0045
astilbin	C4'O9N1	0.03, 0.03, 0.01	0.0012
atorvastin	C1'C2'O5	0.08, 0.10, 0.08	0.0018
β-lapachone	C4'C3'O8	0.08, 0.05, 0.11	0.0005
C6-ceramide	C2'C1'C8	0.03, 0.02, 0.05	0.0015
cannabidiol	C2'C4'C3'	0.08, 0.08, 0.05	0.0034
citicoline	P1O3C6	0.11, 0.01, 0.11	0.0033
cuprizone	N9C1O3	0.08, 0.12, 0.04	0.0168
dexamethasone	O6C2O3	0.05, 0.02, 0.05	0.0011
dexrazoxane	C4N3O5	0.10, 0.13, 0.05	0.0128
embelin	C4'C3'O8	0.04, 0.04, 0.04	0.0020
ethidium	C8O9C2'	0.02, 0.06, 0.08	0.0067
fasudil	C2'N9O5	0.10, 0.09, 0.06	0.0137
fingolimod	C4O3C4'	0.06, 0.11, 0.08	0.0007
geniposide	C2C3'O3	0.09, 0.03, 0.05	0.0053
gliclazide	C3'O3P1	0.05, 0.07, 0.04	0.0174
glucose	C3'O9C4'	0.08, 0.09, 0.06	0.0025
glucose	O9C1'C8	0.00, 0.01, 0.01	0.0008
isofagomine	O5C4'C2'	0.06, 0.07, 0.12	0.0075
levodopa	C4N9C2'	008, 0.11, 0.03	0.0168
licochalcone	C6C5C2'	0.05, 0.10, 0.06	0.0126
loganin	O2C3'O3	0.02, 0.03, 0.02	0.0058
lysophosphatidylcholine	O2O3O5	0.11, 0.08, 0.06	0.0090
magnol	O2C2'O5	0.08, 0.04, 0.05	0.0094
mdivi-1	C4'C3'C2	0.08, 0.07, 0.01	0.0065
metamphetamine	C4'C3'C2	0.05, 0.10, 0.08	0.0041

Continued

metformin	C3'O3O5	0.04, 0.04, 0.04	0.0054
metformin	C2N3C4	0.01, 0.01, 0.01	0.0045
monomethylfumarate	O2C3'O8	0.11, 0.01, 0.10	0.0101
MPTP	C3'C1'N1	0.11, 0.06, 0.12	0.0155
NE52-QQ57	C6N7C3'	0.09, 0.09, 0.05	0.0195
nicotinamide	O3C4'C3'	0.05, 0.06, 0.12	0.0068
nicotinamide	O6C6C4	0.03, 0.07, 0.04	0.0110
nitrovinylbenzoic acid	O8C8C2'	0.05, 0.07, 0.08	0.0077
orientin	C6C5O7	0.03, 0.03, 0.01	0.0026
palmitic acid	C3'C2'C6	0.08, 0.09, 0.03	0.0114
papaverine	C6C2C4'	0.07, 0.09, 0.03	0.0163
paraquat	N1C2C1'	0.03, 0.03, 0.01	0.0046
pentylenetetrazole	C3'C2'O9	0.11, 0.11, 0.07	0.0003
pentylenetetrazole	C4C5N7	0.04, 0.02, 0.03	0.0014
riluzole	C4'C3'O8	0.07, 0.08, 0.06	0.0046
rotenone	O6C6C1'	0.07, 0.07, 0.01	0.0036
schizandrin A	C2C8C2'	0.04, 0.04, 0.05	0.0074
silibinin	O9C1'C6	0.07, 0.05, 0.11	0.0005
sphingosine	C4'C2'O3	0.09, 0.10, 0.11	0.0173
sphingosine-1-phosphate	P1C4'O3	0.12, 0.11, 0.06	0.0091
streptozotocin	09C1'C8	0.02, 0.02, 0.01	0.0050
sulforaphane	C8N9O7	0.02, 0.14, 0.15	0.0072
taraxasterol	C3'C2'N1	0.09, 0.12, 0.05	0.0148
taurine	O307O8	0.06, 0.08, 0.10	0.0059
telmisartan	N7C5C4'	0.04, 0.07, 0.05	0.0065
thymoquinone	O8C3'C4'	0.15, 0.06, 0.10	0.0065
ursolic acid	N9C1'O8	0.05, 0.07, 0.02	0.0009
xanomeline	O5O3N9	0.04, 0.05, 0.04	0.0016
vitamin D3	C3'C2'C2	0.13, 0.06, 0.07	0.0008
Y-27632	C3'C2'C2	0.04, 0.04, 0.03	0.0066

cGMP template (1) in various ways. Paraquat (2) and MPTP (3) are not dissimilar to the phenylpropanamine structure of metamphetamine (4) with fitting-points on both purine and furan rings. Streptozotocin (7) a glucosamine-nitrosourea structure, provides the same fits as glucose (5, 6) and these fitting-points are shared by ethidium (12). In contrast to the fits of glucose, those of pentylenetetrazole (8, 9) do not overlap. The superimposed structures of palmitic



1: cGMP, 2: paraquat, 3: MPTP, 4: metamphetamine, 5: glucose, 6: glucose, 7: streptozotocin, 8: pentylenetetrazole, 9: pentylenetetrazole, 10: palmitic acid, 11: cuprizone, 12: ethidium, 13: rotenone, 14: lysophosphatidylcholine, 15: 6-hydroxydopamine, 16: C6-ceramide, 17: dexamethasone, 18: sphingosine.

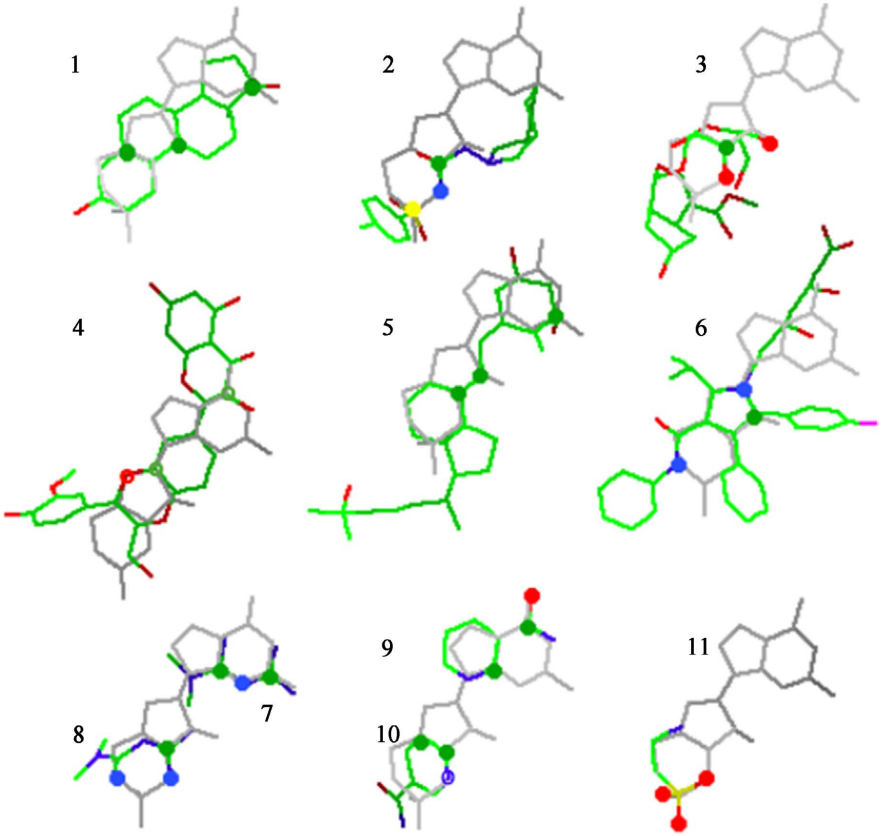
Figure 1. Compounds promoting apoptosis in neurodegenerative conditions: fits of structures to cGMP template (grey).

acid (10) and cuprizone (11) follow the ring contours provided by the cGMP template. Rotenone (13) and dexamethasone (17) have an O6 fitting-point in common, otherwise their fitting profiles are distinct. Ceramide (16) has fit-

ting-points on both purine and furan ring systems, whereas those of lysophosphatidylcholine (14), 6-hydroxydopamine (15) and sphingosine (18) are restricted to the ribose-phosphate moiety. Goodness of fit values for these compound structures (Table 1) range from 0.00 - 0.12 Å (interatomic distance) and 0.0003 - 0.0168 Å (RMS value).

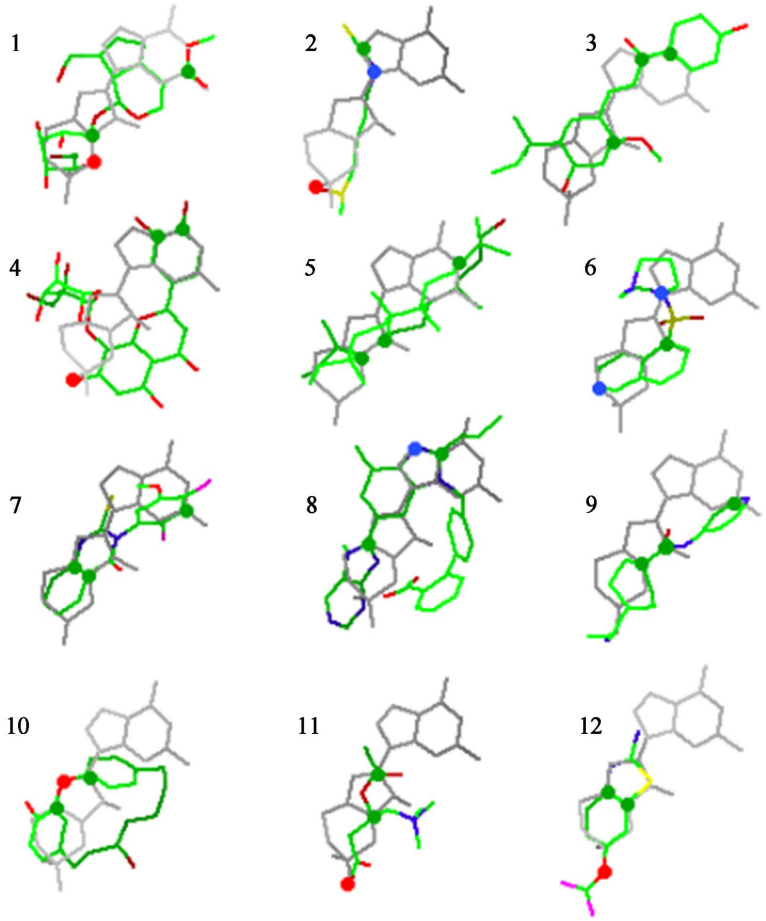
The molecular structures in Figure 2 represent protective compounds used in animal and cell culture models of diabetes. The ribose-phosphate and cyclised ring moieties of the nucleotide template are the foci of these structures, although the degree of superimposition on the cyclised ring is variable; complete for estradiol (1) and vitamin D (5) and significant but partial for the structures of gliclazide (2) and atorvastin (6). Purine ring fitting-points are not evident for several of the structures (2, 3, 6, 11) whereas the smaller structures of metformin (7, 8) and nicotinamide (9, 10) provide two non-overlapping fits to the purine and cyclised rings. Goodness of fit values for these compound structures range from 0.01 - 0.13 Å (interatomic distance) and 0.0005 - 0.0174 Å (RMS value).

Figure 3 compound structures demonstrate protective properties against motor neurone degeneration and oxygen/glucose deprivation in cell culture and animal models. Structures 1 - 9 have fitting-points on both purine and ribose-



1: estradiol, 2: gliclazide, 3: loganin, 4: silibinin, 5: vitamin D, 6: atorvastin, 7: metformin, 8: metformin, 9: nicotinamide, 10: nicotinamide, 11: taurine.

Figure 2. Compounds protecting against apoptosis in diabetic models: fits of structures to cGMP template (grey).

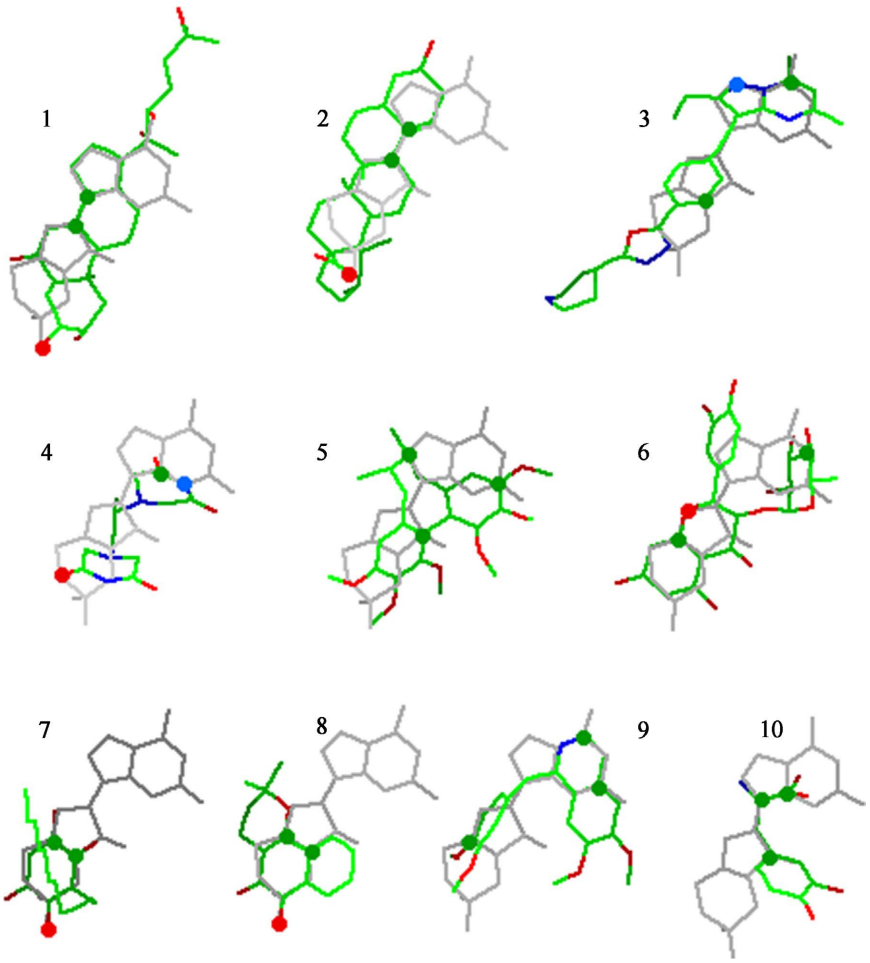


1: geniposide, 2: sulforaphane, 3: licochalone, 4: orientin, 5: taraxosterol, 6: fasudil, 7: mdivi-1, 8: telmisartan, 9: Y-27632, 10: acerogenin, 11: acetylcarnitine, 12: riluzole.

Figure 3. Compounds protecting against apoptosis in motor neurone disease models: fits of structures to cGMP template (grey).

phosphate rings of the cGMP template, whereas fitting-points of structures 10 - 12 are confined to the ribose-phosphate moiety, the main fitting focus of these protective compounds. Glucose moieties, evident within the structures of geniposide (1) and orientin (4) do not necessarily provide fitting-points to the nucleotide template and no single nucleotide fitting-point is essential for a 3-point fit. **Table 1** lists an alternative fit for acetylcarnatine (11) and provides a fitting-value of sulforaphane that is weaker than the other structures. Goodness of fit values for these compounds range from 0.01 - 0.15 Å (interatomic distance) and 0.0026 - 0.0251 Å (RMS value).

The protective compounds relevant to Parkinson's disease, given in **Figure 4**, demonstrate the same fitting characteristics as those in **Figure 2** and **Figure 3**; most fitting-points are on both purine and ribose-phosphate ring systems and all apart from levodopa (10) superimpose partially or completely on the nucleotide cyclised ring. The different fits provided by the steroids 20-hydroxyecdysone (1) and estradiol (**Figure 2**) are exclusive to these structures. The fit of levodopa (also given by tolbutamide but not shown) is included for comparison. In contrast

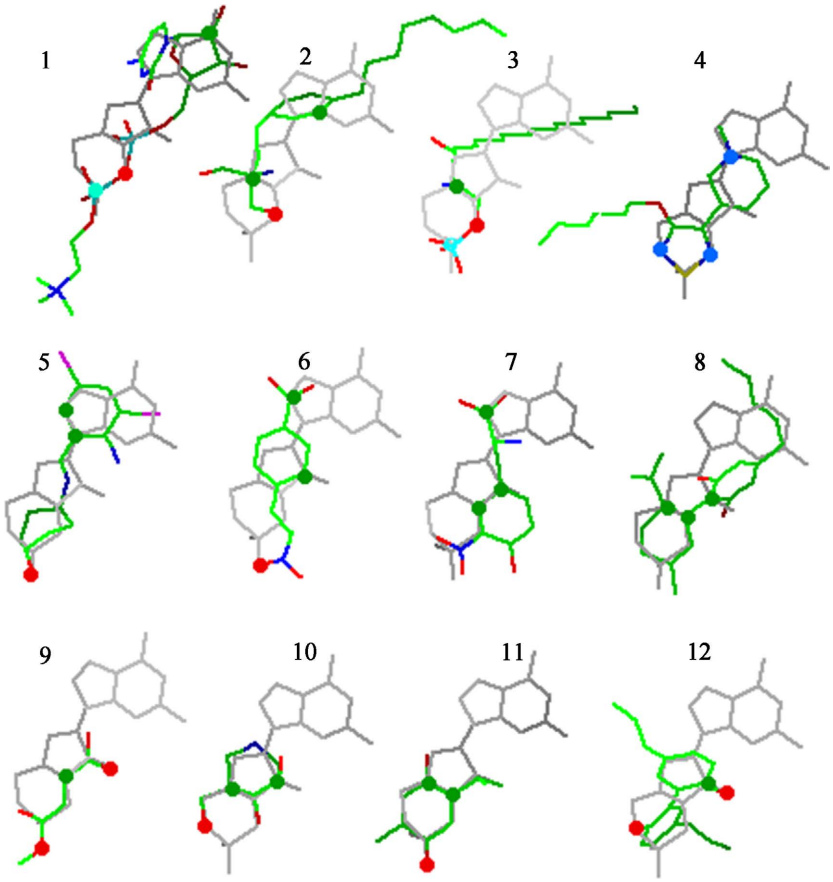


1: 20-hydroxyecdysone, 2: ursolic acid, 3: NE52-QQ57, 4: dexrazoxane, 5: schisandrin A, 6: astilbin, 7: embelin, 8: β-lapachone, 9: papaverine, 10: levodopa.

Figure 4. Compounds protecting against apoptosis in Parkinson's disease models: fits of structures to cGMP template (grey).

to the other structures, the levodopa fit leaves the nucleotide ribose-phosphate ring exposed; levodopa and tolbutamide have apoptosis-inducing properties. Goodness of fit values for **Figure 4** structures range from 0.01 - 0.13 Å (interatomic distance) and 0.0005 - 0.0195 Å (RMS value).

Compounds in **Figure 5** have protective properties against neurodegeneration. Citicoline (1), fingolimod (2), sphingosine phosphate (3), cannabidiol (8), monomethylfumarate (9) and magnol (12) provide benefits in models of multiple sclerosis. Compound structures, 3-nitrotyrosine (7) and cannabidiol aside, fit to different oxygen atoms in the cyclised ring of the cGMP template; a characteristic that differs from compound fits in previous figures. Citicoline and sphingosine phosphate both fit to the cyclised ring phosphate group. The structure of 3-nitrotyrosine, an apoptosis-inducing compound, is included for comparison. The nucleotide ribose-phosphate ring is again the main fitting focus of these neuroprotective compounds, an observation made most obvious by structures 9 - 12. The small changes in the structures of sphingosine phosphate and



1: citicoline, 2: fingolomod, 3: sphingosine phosphate, 4: xanomeline, 5: ambroxol, 6: nitrovinylbenzoic acid, 7: 3-nitrotyrosine, 8: cannabidiol, 9: monomethylfumarate, 10: isofagomine, 11: thymoquinone, 12: magnol.

Figure 5. Compounds protecting against apoptosis in models of neurodegeneration: fits of structures to cGMP template (grey).

sphingosine (**Figure 1**) contribute to their different effects on cell apoptosis and fitting patterns. In contrast, the unrelated anti-apoptotic structures of xanomeline (4) and metformin (**Figure 2**), and of ambroxol (5) and sulforaphane (**Figure 3**) have similar fitting-points. Goodness of fit values for the above structures range from 0.01 - 0.15 Å (interatomic distance) and 0.0003 - 0.0101 Å (RMS value).

4. Discussion

The data demonstrate that the nucleotide relative molecular similarity inherent in neurotoxin structures is more obvious than any similarity between the individual compound structures, an observation that also applies to the neuroprotective compounds investigated in this study. Neurotoxic and neuroprotective structures differ in the fits they provide to the nucleotide template. The former do not occlude the nucleotide cyclised ring, even with fitting-points on that ring. Neuroprotective compounds superimpose over the cyclised ring; fitting points are frequently cyclised ring atoms including O8, with bulky chemical groups ad-

jacent to the ring structure. Several neurotoxic pesticides have been linked to the development of Parkinson's through initiating mitochondrial dysfunction [59] and all compounds in **Figure 1** impact mitochondrial function.

Reduced endoplasmic reticulum stress and oxidative stress mechanisms are responsible for the protective effects of estradiol, vitamin D, loganin, taurine and silibinin on β-cell and Schwann cell apoptosis induced by glucose, streptozotocin and palmitic acid [1] [2] [3] [6]. There is evidence for an abnormality in the regulation of mitochondrial fission by dynamic-related protein 1 (DRP1) in Alzheimer's, Parkinson's and diabetes [12]. Oxidative stress and apoptosis in hippocampal cell cultures are ameliorated by the DRP1 inhibitor mdivi-1 and the diabetic drug metformin [12]. mdivi-1, nicotinamide and glicazide fit to the cGMP template in a similar manner to metformin, taurine and the muscarinic agonist xanomeline. The restricted nucleotide fits of gliclazide and taurine are indicative of the importance of the cyclised ring structure for apoptosis protection. The double fits of protective metformin and apoptosis-inducing PTZ are dissimilar in comparison.

Of the simple neurotoxin compounds used in animal models to induce dopaminergic neurodegeneration, MPTP initiates a high proportion of Parkinsonian symptoms [26]. **Figure 4** demonstrates that the molecular structures of compounds providing protection against MPTP do not compete for the same template fitting-points; only astilbin has 2 common fitting-points with MPTP. The protection afforded by the selective GRP4 antagonist NE52-QQ57 against MPTP-induced apoptosis is attributed to the role of G protein-coupled receptor 4 in mitochondrial-associated apoptosis [39]. Schisandrin A, protective against MPTP in a mouse model of Parkinson's [26], is one of many plant derivatives with an apoptosis-modulating effect on cancer cells. The pro-drug levodopa induces neuron death [60] and has a typical apoptosis-inducing fit to the nucleotide template, whereas its less toxic metabolite, dopamine, is unable to provide the levodopa fit. Higher doses of levodopa given to patients with disease progression may induce dyskinesia. Levodopa and the neurotoxin 6-hydroxydopamine also fit to a cAMP structural template, an observation that may relate to the reported inhibition of adenyl cyclase in levodopa-induced dyskinesia [61]. In regard to the cGMP nucleotide, the aromatic ring of 6-hydroxydopamine provides a fit similar to the sphingosine structure (**Figure 1**).

The symptoms of Parkinson's are not solely attributable to loss of dopamine function, as GMP, GABA and dopamine interact in maintaining normal corticostriatal neurotransmission [62]. Studies using several different experimental approaches demonstrate that cGMP is a key regulator of synaptic strength in the striatum [63]. Low cGMP levels are evident in Parkinson's patients during levodopa-induced dyskinesia [64]. Phosphodiesterase inhibition modulates corticostriatal activity in a 6-hydroxydopamine model of Parkinson's, and inhibition of striatal soluble guanylyl cyclase reverses basal ganglion dysfunction and akinesia [65] [66]. The regulatory effects of cGMP are also evident in other neurodegenerative conditions. Acute relapsing phases of EAE (experimental autoimmune

encephalitis) are characterised by enhanced susceptibility to mitochondrial complex 1V inhibition and ameliorated by compounds acting via the guanylyl cyclase-protein kinase pathway [67]. The benefits of phosphodiesterase inhibitors have been observed in clinical trials on MS patients [68] and in rat models of Alzheimer's disease [69].

Toxin-induced MS models of demyelination using cuprizone, ethidium bromide and lysophosphatidylcholine induce oligodendrocyte apoptosis and neural pathology [28]. These cytotoxins demonstrate relative molecular similarity to cGMP but the template fits of cuprizone and ethidium differ, in that the former is more similar to the palmitic acid fit and the latter shares streptozotocin and ceramide fitting-points. Of the protective agents investigated in MS models, citicoline best matches the fit of cuprizone. Sphingolipids have a role in the development of neurodegenerative diseases via the promotion of ceramide-induced apoptosis [24]. Fingolimod, a sphingosine-1-phosphate receptor modulator, shares template fitting-points with its analogue sphingosine. The fits of monomethylfumarate, isofagomine and thymoquinone structures demonstrate the same cyclised ring focus as sphingosine phosphate. Although oxidative stress and mitochondrial dysfunction are acknowledged as important components of MS pathology, the benefits of MS therapeutics are usually considered in terms of anti-inflammatory and immunological effects [70]. Fumarates are reported to activate anti-oxidative pathways, though the mechanism of this effect isn't clear. In respect of structures, template fits and anti-oxidative properties, fingolimod, xanomeline and ambroxol are comparable compounds. The neuroprotective properties of magnol extend to reversing EAE associated histopathology [40]. 3-nitrotyrosine, a stress marker inducing motor neurone death *in vitro* [29] [58] and anti-apoptotic cannabidiol [41] demonstrate the different fits of neurotoxic and neuroprotective compounds. The former compound leaves the ribose-phosphate group exposed and the latter superimposes an aromatic ring on this site. The fits of 3-nitrotyrosine and neuroprotective sphingosine phosphate differ significantly in their influence on the cGMP phosphate group.

Several compounds with established protective properties against neural cell apoptosis are less associated in the literature with a specific neurodegenerative disease. Xanomeline, orientin, geniposide, licochalcone A, taraxasterol, acetylcarnitine, and atorvastatin all protect neural cells from the effects of oxygen/glucose deprivation [16] [50]-[55]. Citicoline, acerogenin and riluzole protect neural cells from glutamate-mediated cell death [45] [46] [56]. Fasudil and Y-27632 inhibit ROCK protein kinase, a regulator of apoptotic cell membrane blebbing [48]. The cytoprotective properties of the natural antioxidant sulforaphane improve mitochondrial dysfunction [57].

The similar metabolic lesions of oxidative stress and mitochondrial dysfunction described for DPN, Parkinson's and Alzheimer's diseases, concur with reports of enhanced risk factors for the associations of these neurodegenerative conditions [13] [71] [72]. Malfunctions in redox parameters and apoptosis are also characteristics of tumour cells, and so it is unsurprising to find drugs with

efficacy against cancer being applied to neurodegenerative conditions, or to discover that experimental models developed to study different neurodegenerative conditions are responsive to the same compounds. Examples of such pluripotent compounds include resveratrol, carnosic acid, vitamin D and statins [73] [74] [75] [76]. Although neurodegenerative conditions are characterised by neurocellular changes involving complex molecular mechanisms and different clinical symptoms, a fundamental flaw in the control of cell redox parameters may initiate a pathological process that develops clinically in a manner dependent on the cell types involved to become manifest as different diseases. Cells in body tissues are subject to the same oxidative stress mechanisms initiating from chemical toxins, or resulting from deterioration in antioxidant mechanisms provided by protective endogenous compounds. Risk analysis, early intervention and the correction of malfunctioning redox systems may be required in neuroprotective strategies [77]. Molecular similarity within the structures of neurotoxins and neuroprotective compounds relative to cGMP and the established properties of the nucleotide in regulating oxidative stress, intracellular calcium and apoptosis, implicate cGMP and cGMP signaling in the earliest stages of neurodegeneration.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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